Medical Lib.
Apr 15 1922

VOLUME 29 NUMBER 4

ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD
JOSEPH L. MILLER, Chicago
RICHARD C. CABOT, Boston
LOUIS V. HAMMAN, Baltimore
GEORGE DOCK, St. Louis
WARFIELD T. LONGCOPE, New York
W. S. THAYER, Baltimore

APRIL 15, 1922

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

JANUARY, 1922. NUMBER 1

Motor Phenomena Occurring in Normal Stomachs, in the Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically. Lawrence Reynolds, M.D., and C. W. McCluse, M.D., Boston.

Clinical Observations on the Capillary Circulation. S. O. Freedlander, M.D., and C. H. Lenhart, M.D., Cleveland.

The Protein Requirement in Tuberculosis. William S. McCann, M.D. (with the Technical Assistance of Estelle Magill), New York.

Observations on the Use of Quinidin in Auricular Fibrillation. J. A. E. Eyster, M.D., and G. E. Fahr, M.D., Madison, Wis.

Tuberculosis of the Heart, with the Report of Two Cases. Edward Weiss, M.D., Philadelphia.

Observations Following Intravenous Injections of Hypertonic Salt Solutions in Cases of Neurosyphilis. James Wynn, Boston.

A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies. K. B. Gibson, Ph.D., Francis T. Martin, B.S., and Mary Van Rensselaer Buell, Ph.D., Iowa City.

The Nitrogen Requirement for Maintenance in Diabetes Mellitus. Phil. L. Marsh, M.D., L. H. Newburgh, M.D., and L. E. Holly, M.D., Ann Arbor, Mich.

Mycotic Embolic Aneurysms of Peripheral Arteries. de Wayne C. Richey, B.Sc., M.D., and W. W. G. MacLachlan, M.D., C.M., Pittsburgh.

Book Reviews.

FEBRUARY, 1922. NUMBER 2

Tracheal and Bronchial Stenosis as Causes for Emphysema. C. F. Hoover, M.D., Cleveland.

A Study of Microlymphoidocytic Leukemia, with the Report of a Case. Solomon Fineman, M.D., M.A., Minneapolis.

Intracutaneous Reactions in Lobar Pneumonia. George H. Bigelow, M.D., Boston.

Clinical Studies on the Respiration. VIII. The Relation of Dyspnea to the Maximum Minute-Volume of Pulmonary Ventilation. Cyrus C. Sturgis, M.D.; Francis W. Peabody, M.D.; Francis C. Hall, M.D., and Frank Fremont-Smith, Jr., M.D., Boston.

Position and Activities of the Diaphragm as Affected by Changes of Posture. Roy D. Adams, M.D., and Henry C. Pillsbury, M.D., Major, M. C., U. S. Army, Washington, D. C.

Auriculoventricular Rhythm and Digitalis. Henry B. Richardson, M.D., New York.

A Case of Disseminated Miliary Tuberculosis in a Still-Born Fetus. R. C. Whitman and L. W. Greene, Boulder, Colo.

A Convenient Electrode for Experimental Electrocardiographic Work. Carl S. Williamson, M.D., Rochester, Minn.

Book Review.

MARCH, 1922. NUMBER 3

Clinical Studies on the Respiration. IX. The Effect of Exercise on the Metabolism, Heart Rate and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease. Francis W. Peabody, M.D., and Cyrus C. Sturgis, M.D. With the Assistance of Bertha L. Barker and Margaret N. Read, Boston.

Studies in Diabetes Insipidus. Water Balance and Water Intoxication. Study I. James F. Weir, M.D.; E. Eric Larson, M.D., and Leonard G. Rowntree, M.D., Rochester, Minn.

A Hitherto Undescribed Tumor of the Base of the Aorta. George R. Herrmann, M.D., and Montrose T. Burrows, M.D., St. Louis.

Circulatory Compensation for Deficient Oxygen Carrying Capacity of the Blood in Severe Anemias. George Fahr and Ethel Ronzone, Madison, Wis.

Bacillus Acidophilus and Its Therapeutic Application. Leo F. Rettger, Ph.D., and Harry A. Cheplin, Ph.D., New Haven, Conn.

The Efflux of Blood from the Carotid Artery of the Dog and Its Expression by a General Empirical Formula. Halbert L. Dunn, B.A., M.A., Minneapolis.

Study of Blood Sugar Curves Following a Standardized Glucose Meal. W. H. Olmsted, M.D., and L. P. Gray, M.D., St. Louis.

Book Reviews.

Copyright, 1922, by the American Medical Association

Archives of Internal Medicine

VOL. 29 APRIL, 1922 No. 4

OBSERVATIONS ON PAROXYSMS OF TACHYCARDIA *

H. M. MARVIN, M.D., AND PAUL D. WHITE, M.D.
BOSTON

1. *The Frequency of Paroxysms of Auricular Fibrillation.*—The widespread use of instruments of precision in the diagnosis of cardiac arrhythmias during the past few years, and the resulting improvement in diagnosis, have demonstrated that paroxysmal auricular fibrillation is by no means a rare clinical condition. That it is encountered in a certain variable proportion of hospital patients has been pointed out by a number of observers, most of whom have expressed their belief that the condition occurred more commonly than was recognized, but the highest percentage of cases yet recorded is that of Levine,[1] who found that 14.1 per cent. of his group of patients with auricular fibrillation had shown at some time the transient form. This author includes in his series four patients who showed auricular fibrillation only during the transitional stage between auricular flutter and normal rhythm; if these be excluded, his percentage becomes 10.9, which still remains the largest published figure.

In sharp contrast to this comparatively infrequent occurrence, it is our experience that paroxysmal auricular fibrillation is found in private practice with almost the same frequency as the permanent form, and about as often as paroxysmal auricular tachycardia. In a recent series of 250 cases with cardiac symptoms or with signs of heart disease (consultation case of one of us), there were fifteen cases of paroxysmal auricular tachycardia, seventeen cases of paroxysmal auricular fibrillation, eighteen cases of permanent auricular fibrillation, and four cases of paroxysmal flutter. One of the cases of paroxysmal flutter showed also on occasion the coarse type of paroxysmal fibrillation, and is included in both groups.[2] The total number of patients with auricular

* From the Cardiographic Laboratory, Massachusetts General Hospital.

1. Levine, S. A.: Auricular Fibrillation: Some Clinical Considerations, Am. J. M. Sc. **154**:43, 1917.

2. It seems highly probable that paroxysms of flutter and of fibrillation may occur in the same patient at different times more commonly than reports would indicate. Theoretically, such variations might be expected, in view of

fibrillation in this group is thirty-five, and seventeen of these, or 49 per cent., showed the transient form.[4]

Eleven of the seventeen patients with paroxysmal auricular fibrillation were more than 50 years of age (eight were past 60 years). The age incidence in this series is thus in general accord with the observations of Levine,[1] Heard and Colwell,[5] Fox[6] and Robinson.[7] Krumbhaar[8] reported six cases, the patients aged 53, 38, 40, 18, 33 and 35 years, respectively. Our two youngest patients were aged 22 and 27 years, respectively; the etiology of their paroxysms is not clear. Both showed cardiac enlargement on roentgen-ray examination. In contrast to the age incidence of this group of cases, we find that more than two thirds of the patients with paroxysmal auricular tachycardia (eleven out of fifteen) were under 50.

The common types of heart disease in which we have seen the paroxysmal or transient form of auricular fibrillation are the same as those in which the permanent form of arrhythmia is commonly seen. They are most frequently arteriosclerotic (ten of seventeen); less often rheumatic (three of seventeen) and thyroid (two of seventeen). A recent article by Smith[9] has emphasized this close correspondence. Rarely, this paroxysmal type of fibrillation may be found during the course of acute pericarditis; we have seen three such cases (only one included in the present group of 250 cases) and Krumbhaar has reported one case. Severe acute infections (particularly pneumonia), hyper-

---

the ready transitions from flutter to fibrillation after digitalis, and from fibrillation to flutter after quinidin. The recent work of Lewis and his associates,[3] which has demonstrated the common origin of the two conditions in a circus movement in the auricle, lends further support to the belief that one patient may exhibit both mechanisms.

3. Lewis, T.: Observations on Flutter and Fibrillation: Part 2, The Nature of Auricular Flutter, Heart **7**:191, 1920. Observations on Flutter and Fibrillation: Part 9, The Nature of Auricular Fibrillation as It Occurs in Patients, Heart **8**:193, 1921.

4. It is to be remembered that this figure represents the incidence of transient auricular fibrillation among patients seen in a consulting practice, where opportunity has been afforded of seeing them earlier in disease than in the usual hospital practice. It is not, therefore, to be compared with previous reports based on hospital records of patients who presented themselves, as a rule, only when forced to do so by a failing heart. Perhaps in general private practice the ratio of paroxysmal to permanent auricular fibrillation would be found even greater.

5. Heard, J. D., and Colwell, A. H.: Transient Auricular Fibrillation, Penn. M. J. **24**:59 (Nov.) 1920.

6. Fox, G. H.: The Clinical Significance of Transitory Delirium Cordis, Am. J. M. Sc. **140**:815, 1910.

7. Robinson, G. C.: Paroxysmal Auricular Fibrillation, Arch. Int. Med. **13**:298 (Feb.) 1914.

8. Krumbhaar, E. B.: Transient Auricular Fibrillation, Arch. Int. Med. **18**:263 (Aug.) 1916.

9. Smith, F. M.: Clinical Observations on Paroxysmal Auricular Fibrillations and Flutter, Am. J. M. Sc. **162**:13, 1921.

thyroidism and digitalis in large doses, may be responsible for the onset of the new mechanism. It seems highly improbable that nervous stimulation alone may be responsible for the clinical condition; no clear-cut case is on record, although three of our cases were somewhat suggestive when first seen.[10] In our experience, and in the present series, permanent damage or severe toxicity have been the basis for paroxysms of auricular fibrillation.

The one patient mentioned above who showed at various times paroxysms of auricular flutter and of coarse auricular fibrillation has been under observation for a period of seven years, during which time she has been followed carefully by clinical, roentgen-ray and electrocardiographic observations. One of her electrocardiograms has been published.[11] This patient has shown no important symptoms at any time except during the attacks, she has no murmurs that can be distinguished, and she has worked as a nurse for six years with only four days off duty because of her cardiac condition in spite of very frequent paroxysms. She is now in good health. A cervical rib was removed from the right side of the neck in 1915 and was followed by considerable improvement. A teleroentgenogram of the heart in 1915 showed considerable enlargement; a similar plate taken six years later showed the same degree of enlargement, in the same chambers, notwithstanding frequent paroxysms of tachycardia in the interval.[12]

2. *The Diagnosis of Paroxysmal Tachycardia of Ventricular Origin.*—Within the past few years there has been considerable interest manifested in the subject of paroxysmal tachycardia due to ectopic impulses arising in the ventricular tissue. Although a number of reports of such instances have been published, Robinson and Herrmann[14] in a recent review were able to find only six undoubted instances, and six which were probable, in which the pacemaker responsible for the new rhythm lay in the ventricles. These authors have called attention to the necessity of obtaining electrocardiograms,

10. Nervous stimulation may be and often is, of course, the exciting factor in producing paroxysmal auricular fibrillation in a diseased heart.

11. White, P. D., and Stevens, H. W.: Ventricular Response to Auricular Premature Beats and to Auricular Flutter (Fig. 5), Arch. Int. Med. **18**:712 (Nov.) 1916.

12. Another patient who has shown paroxysmal auricular tachycardia very frequently between 1914 and 1921 has not been incapacitated at all, and is in good health at the present time. He also shows cardiac enlargement of unknown cause. He has been reported as an unusual case of paroxysmal auricular tachycardia,[13] an exception to the general rule of an absolutely abrupt onset and offset of the attack, but nevertheless an undoubted instance of paroxysmal auricular tachycardia, possibly of nomotopic type.

13. White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**:420 (April) 1920.

14. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, Heart **8**:59, 1921.

and have included in their list only those cases from which such curves have been published. In order that the diagnosis may be established beyond question, they direct attention to the following requirements:

(1) The electrocardiogram must give definite indications that the cardiac impulses producing the high ventricular rate are arising in the ventricles, and this can be shown most clearly when a succession of auricular impulses can be made out, occurring independently of, and at a slower rate than, the complexes of ventricular origin. (2) The ventricular complexes must be abnormal in form. (3) The presence of isolated ectopic ventricular beats between paroxysms is in favor of the tachycardia being of ventricular origin, especially if the ectopic beats and those composing the paroxysms are of similar form.

To the six cases previously reported, Robinson and Herrmann have added four, bringing the total number of undoubted cases to ten. It has seemed to us worth while to report a further instance of this comparatively rare type of tachycardia, partly to increase the number of recorded cases, but chiefly to call attention to the possibility of error in making the diagnosis, even with electrocardiograms, unless control records have been obtained from the patient between paroxysms. Under a certain condition, which we shall illustrate, it is possible to obtain records of auricular paroxysms which resemble closely those of ventricular origin.

The patient from whom the electrocardiograms shown in Figures 1, 2, 3 and 4 were obtained was a young woman, aged 21, whose past history was uneventful, except for the occurrence of diphtheria and pneumonia in early childhood and occasional mild attacks of tonsillitis during several successive winters. There had been no symptoms of cardiac disease whatever preceding the onset of the paroxysms of tachycardia; the patient had been attending business school for two years and had taken daily walks of several miles for exercise. Her first paroxysm occurred six weeks prior to her entry to the hospital, as she was stooping to pick something from the floor. It lasted for approximately two minutes, during which time she felt dizzy, her head seemed "hot and swollen," and she was conscious of the tachycardia. The attack ended as suddenly as it had begun, but a second one occurred two hours later and lasted for approximately fifteen minutes. During this second attack her symptoms were as before, but in addition there was marked shortness of breath, which was a feature of all subsequent attacks. After the first day there was a period of freedom for about two months, when the attacks recommenced, and it was during this second period of paroxysms that the following records were obtained.

Figure 1 is an electrocardiogram obtained April 7. Leads I, II and III are shown, and the only abnormality in the curves is a single premature beat arising in the ventricle, which is recorded in Lead II. April 21, we were fortunate in securing the onset of one of her numer-

ous paroxysms (Fig. 2). The plate shows three strips of Lead II, and satisfies in itself all the requirements mentioned by Robinson and Herrmann for the diagnosis. Isolated ectopic beats of ventricular origin are seen in A and B, and these are similar in form to the beats which compose the succeeding paroxysm. The ventricular complexes are highly abnormal in form. Finally, auricular complexes occur in B after every second ventricular beat, the rate of the ventricles being 262.5 per minute and that of the auricles one half this rate. Similar curves, in which the auricles beat at exactly half the rate of the ventricles, P waves appearing at corresponding points on every second ventricular complex, have

Fig. 1.—Electrocardiogram of M. R. Leads I, II and III. Normal complexes throughout except for one ventricular premature beat in Lead II. (In this and all succeeding electrocardiograms, distances between ordinates represent 0.2 second, distances between abscissae 10^{-4} volts.)

been published by Hart,[15] and more recently by Robinson and Herrmann [14] (their Figs. 9, 11 and 13). There is a close resemblance between Hart's Figure 4 and our Figure 2, except that the R waves in our illustration show notching at the tip and the P waves are more prominent than in Hart's case. It is to be noted that during the brief part of the paroxysm shown in B the rate is not absolutely regular, nor are the complexes precisely alike. The time intervals, as measured from peak

15. Hart, T. S.: Paroxysmal Tachycardia, Heart 4:128, 1912.

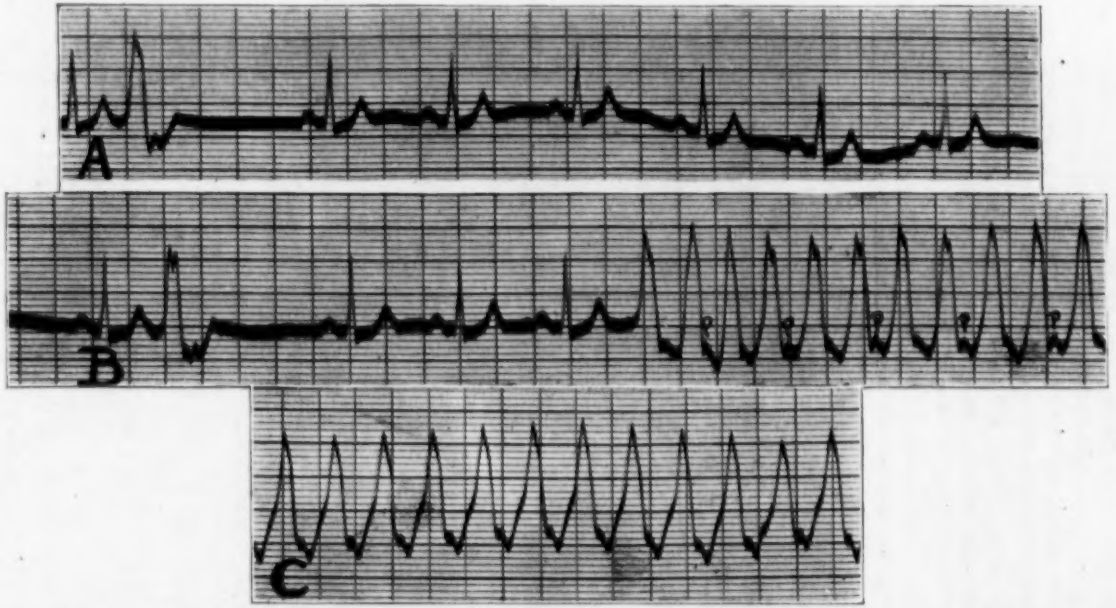


Fig. 2.—Electrocardiogram of M. R. Lead II. Ventricular premature beats in A and B. Onset of ventricular paroxysm in B. Note the presence of auricular waves (P) after every alternate ventricular beat in B. Rate in B, 262 per minute; in C, 220.

to peak of the R waves in seconds are as follows: 0.257, 0.198, 0.212, 0.237, 0.243, 0.243, 0.243, 0.253, 0.245, 0.248. The variation in rate, as shown by these intervals, is largely confined to those beats which initiate the new rhythm; from the fourth beat onward the greatest variation from cycle to cycle is 0.010 second. Thus the rate for the entire stretch of the paroxysm is 262.5, but the rate for the last eight beats is 250. The difference in form of the complexes is apparently of a progressive nature; the second and third beats, for instance, are practically free from notching or slurring of the ventricular complex, the succeeding five beats show very definite slurring of the upstroke of R and notching of the beginning of the downstroke, while the last

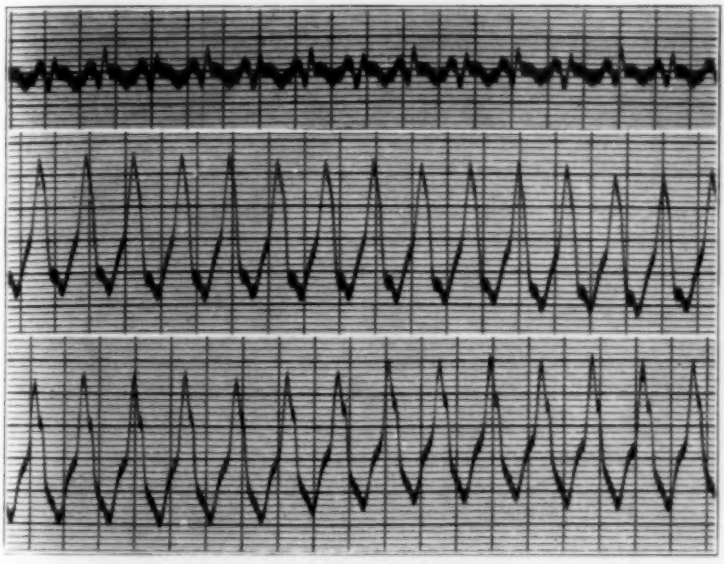


Fig. 3.—Electrocardiogram of M. R. Leads I, II and III, taken during a paroxysm of tachycardia of ventricular origin, in which the rate is 209 in Leads I and III, and 225 in Lead II.

three recorded complexes apparently foreshadow the final form which is to be assumed, in which a heavy slurring of the upstroke and a slighter degree of slurring of the downstroke of R appear as the prominent features.

The lower part of the figure, marked C, was taken within a few seconds after B and shows the form of ventricular complex which characterized the second lead in all subsequent electrocardiograms. It will be noted that the P waves, which appeared so prominently after every second ventricular complex in B, have now almost disappeared.

Fig. 4.—Electrocardiogram of M. R. Lead II. First half of curve shows normal rhythm interrupted by two ventricular premature beats. Just after the second premature beat there is a series of five beats constituting a paroxysm of auricular tachycardia, in which the rate is 125 per minute. Rate of normal rhythm, 75 per minute.

The last feature of the ventricular paroxysms to which attention should be directed is shown in Figures 2 and 3, and consists of the change of rate between the early and later parts of the paroxysm. Thus in Figure 2 the rate in B is 250 or 262.5, according as we include or exclude the first three beats, while in C, taken a few seconds later, the rate is only 220. Similarly, in Figure 3, the rate in Lead II is 225 per minute, while in Leads I and III the rate is from 209 to 211. These two figures are from different paroxysms on the same day.

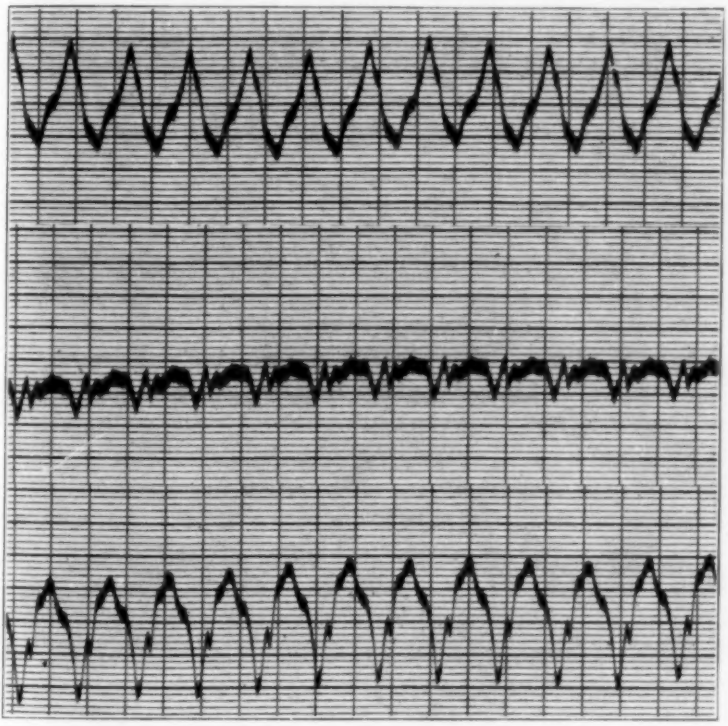


Fig. 5.—Electrocardiogram of L. K. Leads I, II and III. Taken during a paroxysm of tachycardia, in which the rate was 190 per minute. Note the general resemblance between Leads I and II of this figure and Leads II and I, respectively, of Figure 3.

The same patient showed also unusual paroxysms of auricular origin. A plate taken just after that reproduced in Figure 2 and just before that in Figure 3 recorded two such paroxysms, only one of which is here shown (Fig. 4). This curve is from Lead II, and shows in its early part complexes of normal form, with a rate of 75 per minute.

In the middle of the curve are seen two exactly similar premature beats arising in the ventricle. Immediately following the second of these premature beats there occurs a short paroxysm of tachycardia consisting of five beats, in which the normal sequence of chamber contraction is

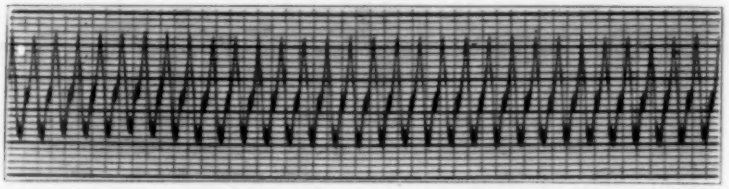


Fig. 6.—Electrocardiogram of L. K. Lead I, taken with plate traveling slowly. Same paroxysm as that shown in preceding figure.

Fig. 7.—Electrocardiogram (Leads I, II and III) of L. K., showing normal rhythm, the ventricular complexes of which are typical of those associated with defective conduction along the right branch of the A-V bundle. Rate, 100 per minute. Ventricular complexes are similar to those in Figure 5.

maintained.[16] The rate is 125 per minute. After the conclusion of the paroxysm, the rate falls at once to its original level.

This case, then, is one in which there have been recorded at different times isolated ectopic beats of ventricular origin, paroxysms of tachycardia of ventricular origin, and paroxysms of tachycardia in which

16. The P wave of the paroxysm is slightly higher than the normal P.

the pacemaker lay in the auricles. In at least one instance, the rate for the first few beats of the ventricular paroxysms was higher than the rate subsequently maintained. In the only instance where the onset of the new rhythm was recorded, there was a slight, progressive change in the form of the first eight ventricular complexes.

By way of contrast to the above example of paroxysms of tachycardia arising in the ventricle, is an electrocardiogram (Fig. 5) from another case which at first sight appears also to be of ventricular origin. Leads I and II of this figure, for example, are quite similar in form to Leads II and I, respectively, of Figure 3. (Corresponding leads cannot be compared because of obvious gross differences.)[17] The general outline of each complex is that of an ectopic beat arising in the ventricle. This appearance is even more striking in Figure 6, which is from Lead I of the same patient, taken with the plate traveling at a slower rate.

That this paroxysm does not owe its origin to impulses arising in the ventricle, however, is made apparent at once by inspection of

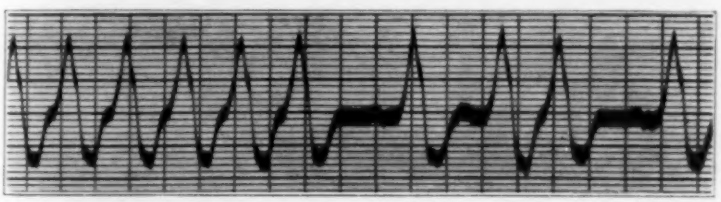


Fig. 8.—Electrocardiogram of L. K. Lead I. The end of a paroxysm is recorded. Note that the first, second and fourth ventricular beats after the end of the tachycardia are in response to impulses from the normal supraventricular focus, yet are similar in all details to the beats composing the paroxysm.

Figure 7, which was obtained about five minutes after Figure 6, and shows the normal rhythm. The three leads are given, and a comparison of this curve with that in Figure 5 shows that the ventricular complexes in both are similar in all three leads and we know them to be of supraventricular origin because in Figure 7 each ventricular beat is preceded by an auricular wave. This electrocardiogram is of the type associated with defective conduction along the right branch of the A-V bundle.

Further proof of the auricular origin of the paroxysm is obtained from Figure 8, in which the termination of a paroxysm is shown. The first, second and fourth beats after the end of the tachycardia are preceded by waves due to auricular activity, and are clearly to be

17. As a matter of fact these very differences would help to differentiate the two conditions, Figure 5 being much more likely an example of intraventricular block.

considered as ventricular responses to impulses from the auricles, yet these ventricular responses are in all respects similar to the beats composing the paroxysm.

It would be impossible to assert with confidence that the paroxysmal tachycardia shown in Figure 5 is of auricular origin without the further knowledge obtained from other records. From the standpoint of accurate diagnosis and a more complete understanding of the electrical events in the heart associated with tachycardias of paroxysmal nature, it is important to make this differentiation.

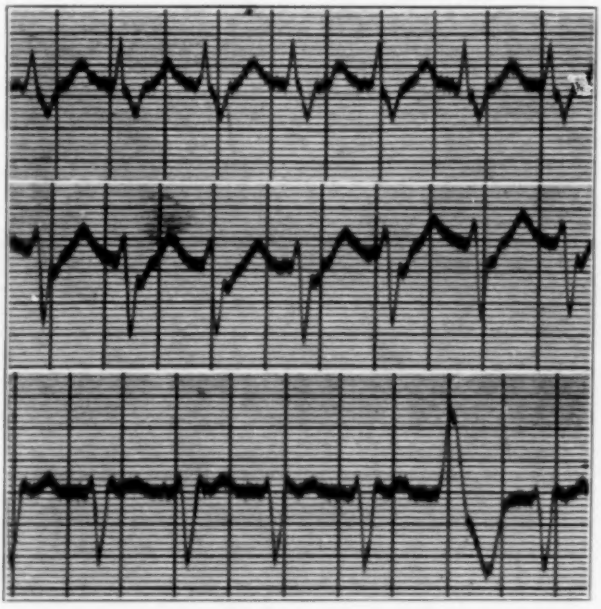


Fig. 9.—Electrocardiogram of E. J. H. Leads I, II and III. Paroxysmal auricular tachycardia. An ectopic beat arising in the ventricle is shown in Lead III. Note that it does not disturb the dominant rhythm.

Lewis [18] has called attention to the possibility of sudden interference with conduction in one branch of the A-V bundle during the period of rapid heart action, and has published a record illustrating aberration only during the paroxysm. Such curves, of course, are similar to those obtained from patients with pre-existing bundle branch block, for the mechanism of their production is exactly alike. Lewis concludes that "in the human subject, paroxysms presenting anomalous ventricular

18. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat. New York, R. Hoeber, 1921, p. 259.

complexes may be produced in one of two ways; these paroxysms either arise in the ventricle itself, or, arising in the auricle, the excitation wave pursues an abnormal ventricular course." This abnormal ventricular course may be due to transient interference with conduction, as in his case, or to permanent interference, as in the case reported above. Reference has already been made [11] to an electrocardiogram published by one of us in 1916, which shows the sudden development of aberration of the ventricular complexes during a paroxysm of auricular flutter.

3. *The Occurrence of Ectopic Ventricular Beats in Auricular Paroxysmal Tachycardia.*—The interruption of paroxysms of auricular tachycardia by ectopic beats arising in the ventricle is of rare occurrence; we have been able to find but one published electrocardiogram illustrating such an event.[19] We have recently seen a case exhibiting ectopic beats with such frequency as to make it one of considerable interest.

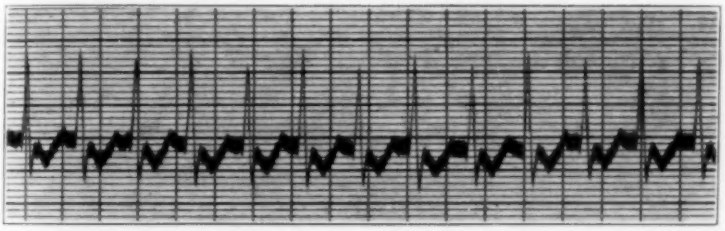


Fig. 10.—Electrocardiogram of J. D. S. Paroxysmal auricular tachycardia. Rate 200. Alternation in size of the QRS complexes is shown.

The patient from whom the curve shown in Figure 9 was obtained was a laborer, aged 57 years, who had been subject to attacks of tachycardia for about three years. The paroxysms occurred usually three or four times a day, for from two minutes to several hours. His only symptom during the attacks was slight palpitation, which had never been of sufficient severity to cause him to stop his work for even a few minutes. An electrocardiogram taken between attacks showed ectopic ventricular beats similar to those which appeared during the attacks, and indicated also partial A-V heart block (the P-R interval measuring 0.233 seconds) and intraventricular block.

Figure 9 was taken during an attack in which the heart rate was 166.6 per minute. It shows one ectopic ventricular beat. Several such beats were recorded during the paroxysm. It is to be noted that the ectopic beat does not disturb the rhythm; it occurs almost at the precise

19. Agassiz, C. D. S.: Paroxysmal Tachycardia Accompanied by the Ventricular Form of Venous Pulse, Heart **3**:193, 1912.

instant when a beat was to be expected, and the beat which follows falls at its proper point. In other words, the same features mark a ventricular premature beat in paroxysmal auricular tachycardia as in the normal rhythm arising in the sino-auricular node; in both instances, the distance between the complexes embracing the ectopic beat measures the same as that between any two rhythmic beats.

This case is recorded because of the rarity of such published curves and because it is of some importance to recognize that the finding of

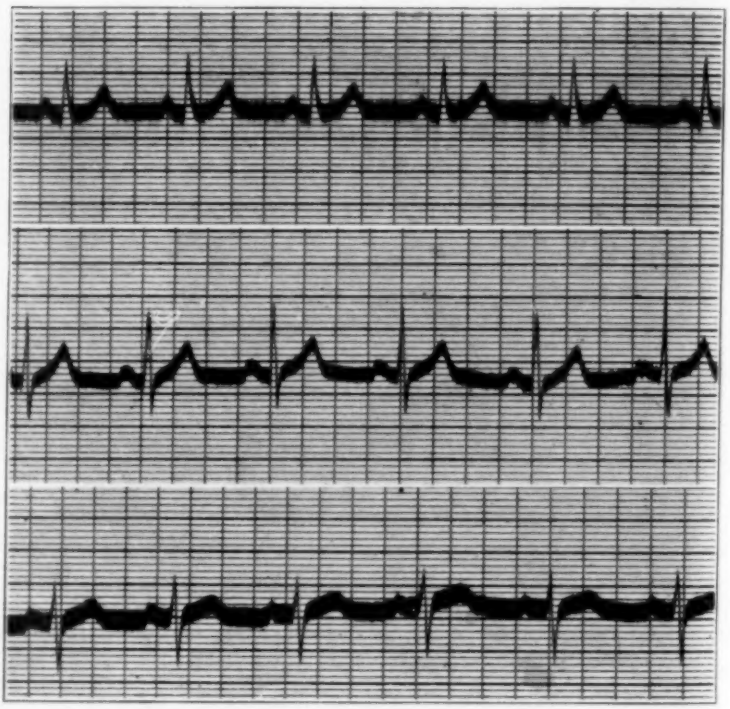


Fig. 11.—Electrocardiogram of J. D. S. Normal rhythm from same patient whose previous record is shown in Figure 10.

ventricular premature beats in a case which presents the features of auricular paroxysmal tachycardia does not militate against that diagnosis. Among the records of more than thirty cases of auricular paroxysmal tachycardia in the files of our laboratory, this is the only instance in which ventricular ectopic beats have been found in the midst of a paroxysm.

4. *Alternation of the R Waves in Paroxysmal Tachycardia.*—Alternation in the amplitude of the radial pulse in cases of paroxysmal

tachycardia occurs with such frequency that it is no longer regarded as unusual or important. Alternation in the height of the R waves in this condition, however, is not common, in so far as one may judge by published records. There have been many curves showing variation in amplitude without alternation, although the vast majority of cases exhibit complexes which are precisely alike in size and shape over long periods. Lewis has placed on record an excellent example of simultaneous alternation of the R waves of the electrocardiogram and the radial pulse, in which the large ventricular complexes correspond to the small pulse waves.[19] Hart [15] has recorded a striking instance of this condition, his curves being obtained from a case of paroxysmal tachycardia of ventricular origin.[20]

The electrocardiogram shown in Figure 10 represents Lead II. The rate is 200 per minute. The patient from whom it was obtained was subject to paroxysms of the usual description, and the only feature of interest in the curve, other than the alternation, is its close resemblance to auricular flutter. A tracing taken after the paroxysm showed curves which were normal in all respects (Fig. 11 showing Leads I, II and III).

SUMMARY

1. Paroxysmal auricular fibrillation is a common type of paroxysms of tachycardia, and is seen in practice as frequently as paroxysmal auricular tachycardia and permanent auricular fibrillation.

2. Paroxysmal auricular fibrillation is found most frequently in old age, the result of cardiosclerosis. It is also found in rheumatic and thyroid hearts, in acute pericarditis, severe acute infections, and following digitalis.[21]

3. Paroxysms of tachycardia may occur at frequent intervals for years without incapacitating the subject and without increasing the degree of cardiac damage appreciably.

4. Paroxysmal tachycardia of ventricular origin is very rare Another case is added to the ten undoubted cases already reported.

5. Electrocardiographic study is essential in the accurate diagnosis of ventricular paroxysmal tachycardia, and even with electrocardiograms the condition must be differentiated from auricular paroxysmal tachycardia with bundle branch block.

6. Ventricular ectopic beats may occur in auricular paroxysmal tachycardia without disturbing the dominant rhythm.

7. Rarely, alternation of the Q R S complexes of the electrocardiogram may be found in paroxysmal tachycardia. (Alternation of the radial pulse in this condition is common.)

20. Lewis, T.: Mechanism of the Heart Beat, 1911, p. 274.
21. It also has been reported after other poisons.

RENAL GLYCOSURIA *

D. S. LEWIS, M.D.
MONTREAL, CANADA

There are four cardinal points in the diagnosis of this interesting anomaly: (a) a glycosuria without hyperglycemia; (b) little, if any, relationship between the carbohydrate intake and the amount of glucose excreted in the urine; (c) the absence of the signs and symptoms characteristic of diabetes mellitus, and (d) a long period of observation during which the patient shows no tendency to develop diabetes mellitus. Joslin [1] lays particular stress on the last criterion, which is the most difficult to carry out. A critical review of the literature is made by Goto,[2] Bailey,[3] Strouse [4] and Lewis and Mosenthal.[5] When preparing data connected with the report in 1915, Lewis and Mosenthal found less than ten cases which were described in sufficient detail to warrant their acceptance as instances of true renal glycosuria, but since that time at least nine other cases [6] have been noted. With the more careful observations of the blood sugar this depression of the "leak point" for glucose is being recognized with greater frequency.

In this paper a further note is recorded on the case reported in 1915 [5] and studies of two other instances observed in the metabolism clinic of the Royal Victoria Hospital are presented in some detail. The clinical findings in the first patient may now be said to fulfill all four requirements as he has been observed for a period of six years; the second and third cases which have been observed for twelve and fifteen months, respectively, can be regarded as answering the first three tests, but a final decision will not be possible without a further period of observation.

Methods Employed.—Sugar identified as glucose, by fermentation; osazone crystals; and synchronous determinations of the amount of sugar by polariscopic and copper reduction methods. Urinary sugar: Benedict's standard quantitative methods. Blood sugar: Lewis-Benedict method, unless otherwise stated in the text.

---

* From the Metabolism Clinic of the Royal Victoria Hospital.

1. Joslin, E.: Treatment of Diabetes Mellitus, Philadelphia, 1917, p. 64.
2. Goto, K.: Alimentary Renal Glycosuria, Arch. Int. Med. **22**:96 (July) 1918.
3. Bailey, C. V.: Renal Diabetes, Am. J. M. Sc. **157**:221, 1919.
4. Strouse, S.: Renal Glycosuria, Arch. Int. Med. **26**:768 (Dec.) 1920.
5. Lewis, D. S., and Mosenthal, H. O.: Renal Diabetes, Bull. Johns Hopkins Hosp. **27**:133, 1916.
6. Beard, H., and Grave, F.: Renal glycosuria, Arch. Int. Med. **21**:705 (June) 1918. Allen, F. M.; Wishart, M. B., and Smith, L. M.: Three Cases of "Renal Glycosuria," Arch. Int. Med. **24**:523 (Nov.) 1919. Paullin, J. E.: Renal Glycosuria, J. A. M. A. **75**:214 (July 24) 1920. Marsh, P.: Renal Glycosuria, Arch. Int. Med. **28**:54 (July) 1921.

REPORT OF CASES

CASE 1.—W. P. W.[6] (medical No. 34774), was first studied in September, 1915. On admission to the Johns Hopkins Hospital his urine contained 2.06 per cent. sugar, and the daily output averaged 25 gm., with a blood sugar ranging from 0.08 to 0.11 per cent. He gave a normal curve following the ingestion of 100 gm. glucose. Further studies by Mosenthal, in 1916, confirmed the findings. In August, 1921, the patient reported that he had continued in excellent health since his discharge from the hospital. He had gained 12 pounds in weight; he had survived a severe "flu" infection, and was taking a full and unrestricted diet. His urine still contained about 2 per cent. sugar, but he had no thirst, polyuria, or any other symptoms of diabetes mellitus.

The following data of recent studies on this individual have been supplied by Dr. F. M. Hanes of Winston-Salem, N. C., and prove that his condition has shown no essential change. The diagnosis made in 1915 has been verified by the subsequent course of the case.

The functional condition of the kidney has attracted considerable attention in renal glycosuria. Klemperer[7] in his first description of what he termed "renal diabetes," stated that the sugar always disappeared from the urine with the onset of a nephritis. On the other

TABLE 1.—RESPONSE OF BLOOD SUGAR TO 132 GM. GLUCOSE

June 8, 1921	Blood Sugar, per Cent.	Remarks
Fasting	0.09	After 24 hours fasting
First hour	0.15	
Second hour	0.12	
Third hour	0.10	

The urine passed during the twelve hours preceding the test contained 3.5 per cent. sugar (Benedict).

hand, Lüthje,[8] Tachau[9] and Naunyn[10] suggested a direct causal relationship between the nephritis and the glycosuria, and the first two gave examples of proved renal glycosuria in which the onset seemed to be associated with the appearance of a nephritis. Frank[11] has described a glycosuria following the toxic nephritis produced by mercury, uranium, chromium and cantharadin, but there has been little evidence of severe kidney disease in a majority of the reported cases. Bailey[3] described one case of severe parenchymatous nephritis, with a renal glycosuria. The blood sugar was comparatively high, and after 75 gm. glucose it rose to 0.4 per cent., returning to the fasting level

7. Klemperer, G.: Ueber regulatorische Glykosurie und renalen Diabetes, Berl. klin. Wchnschr. **33**:571, 1896.
8. Lüthje, H.: Beitrag zur Frage des renalen Diabetes, München. med. Wchnschr. **38**:1471, 1901.
9. Tachau, H.: Beitrag zum Studium des Nierendiabetes, Deutsch. Arch. f. klin. Med. **104**:448, 1911.
10. Naunyn, B.: Der Diabetes Mellitus, Wien., 1906, p. 136.
11. Frank, E.: Ueber experimentelle u. klinische Glykosurien renalen Ursprungs, Arch. f. exper. Path. u. Pharmakol. **72**:387, 1913.

six hours after the meal. This, he states, is a type of curve often seen in nondiabetic cases of nephritis. In this patient the sugar output was remarkably constant, and there was no sign of a true diabetes. Mosenthal and Lewis [12] also report a case of arteriosclerosis and primary contracted kidney, in which a glycosuria appeared while under observation. This patient excreted 22 per cent. of phthalein in two hours, and his blood urea was 0.749 gm. per liter. With a fasting blood sugar of 0.10 per cent., the urine contained 0.13 per cent. sugar, and after the ingestion of 100 gm. glucose the blood sugar rose to 0.26 per cent. in 90 minutes, and returned to the fasting level at the end of three hours.

The following cases are examples of this type of renal glycosuria.

Case 2.—May 5, 1920, T. C., (metabolism No. 50), Chinese boy, aged 18.

History.—About four weeks before admission he had a chill and fever. He passed very little urine. His legs began to swell, and he had to stop work. The swelling gradually spread to his trunk, arms and face. No further history was obtainable. He was admitted to hospital May 9 and transferred to the Metabolism Clinic May 21.

Physical Examination.—Temperature, 98; pulse, 70; respiration, 20 (on admission). Patient was an adult Chinese of about stated age. He lay comfortably in bed. There was marked general anasarca; pupils equal and active; teeth in fairly good condition; tonsils not enlarged; tongue coated; no general glandular enlargement; thyroid not enlarged; no signs of hyperthyroidism. The chest wall was edematous. There was a bilateral hydrothorax and many moist râles were heard over both lungs. The heart was regular in rhythm, and extended 7 cm. to the left of the midline. The sounds were well heard. There were no murmurs or accentuations. The vessel walls were not thickened. Blood pressure: 110/65. The abdomen was tense; the walls were edematous; there was a marked ascites; the liver and spleen were not palpable. The genitalia were much swollen, there was no urethral discharge. The reflexes were active. The eyegrounds were normal.

Urine: Acid; cloudy; specific gravity, 1.026; albumin, 20 gm. per liter; no sugar. Microscopic Examination: Granular, hyalin and fatty casts. White blood cells and an occasional red blood cell.

Tests of Kidney Function.—Blood urea, 0.585 gm. per liter; plasma chlorids, 5.65 gm. per liter; phthalein tests, 8 per cent. in two hours.

Blood: Wassermann test negative. Red blood cells, 5,910,000; white blood cells, 5,600; hemoglobin, 85 per cent. (Talquist).

Diagnosis.—Chronic diffuse nephritis; general anasarca.

Diary.—In view of the severity of the nephritis the patient was kept in bed on a salt-poor diet, with an average daily carbohydrate intake of 125 gm. His condition gradually improved, and he lost 16 kilos in weight, but with an increased diet his edema returned and his general condition became much worse. At this time an estimation of the blood proteins showed a globulin-albumin ratio of 3.61 : 1.30, which is a complete reversal of the usual proportions. In view of Epstein's [13] reports, the diet was changed September 10, to one with

12. Mosenthal, H. O., and Lewis, D. S.: The D : N Ratio in Diabetes Mellitus, Bull. Johns Hopkins Hosp. **28**:187, 1917.

13. Epstein, A. A.: Oedema in Chronic Nephritis, Am. J. M. Sc. **154**:638 (Nov.) 1917.

low fat and relatively high protein values. There was little change in the water balance, but the total nonprotein nitrogen of the blood mounted from 40 mg. per hundred c.c. to 89 mg. per hundred c.c. in six days, and the diet was discontinued soon afterward. Suddenly, September 22, a glycosuria appeared. The first day the output was 6.99 gm.; the next day it was 7.39 gm., and for the succeeding eight months sugar was absent in only five twenty-four-hour specimens, and in individual specimens of six other days. During this entire period the output has never exceeded 16.8 gm., and it has been between 5 and 10 gm. 151 times in a total of 230 determinations (Table 2), while the concentration in the urine has been from 0.5 to 0.75 per cent. in two of every three examinations. In other words, the output and concentration have shown a high degree of constancy.

TABLE 2.—Range of Concentration and Total Excretion of Sugar in Urine

Concentration in Urine, per Cent.	Number of Analyses	Per Cent. of Total No.	Output in Gm. per Day	Number of Analyses	Per Cent. of Total No.
Above 0.75	38	16.5	Above 10.0	38	16.5
0.75 – 0.50	151	65.7	10.0 – 5.0	151	65.7
Below 0.50	41	17.8	Below 5.0	41	17.8

TABLE 3.—Independence of Carbohydrate Intake and Output

	Diet			Sugar in Urine	
Date, 1920	Protein	Fat	Carbohydrate	Per Cent.	Gm.
Nov. 2	41	42	174	0.86	6.45
3	49	57	209	0.51	3.82
4	39	39	144	0.82	3.74
5	20	21	87	0.60	2.70
6	46	52	204	0.43	2.79
7	46	53	204	0.40	6.68
8	46	52	204	D. 0.28	1.12
				N. 0.00	0.00
9	46	53	204	0.51	5.71
10	28	30	138	0.65	6.82
11	54	61	135	0.43	3.01

D., day specimen; N., night specimen.

Again, the total output of glucose seems to be independent of the carbohydrate intake, the higher rates of excretion often being associated with the lower diets and vice versa. Table 3 will serve to illustrate the independence of intake and output.

Similarly, his excretion varies from 0 to 8.16 gm. during the period from November 16 to December 16 with an unchanged diet which contained protein, 50 gm.; fat, 57 gm., and carbohydrate, 234 gm. Throughout the period of observation the changes in the output are featured by their sudden onset and disappearance. In Table 3 the output is 6.68 gm. one day, 1.12 gm. the next day, then sugar free for twelve hours, and on the following day is reestablished at its old level of 5.71 gm. On the other hand, during any particular day the rate of

excretion from hour to hour seems to be very constant. Two hourly collections are presented in Table 4, and show a maximum variation in concentration of only 0.16 per cent., and an hourly output from 0.50 to 0.36 gm.

In September, 1921, he was studied again, and at this time he was fasted for three days before becoming sugar free. On a gradually increasing carbohydrate diet traces of sugar reappeared with 30 gm. carbohydrate given as green vegetables, and a measurable quantity (0.18 per cent.), with a diet containing 40 gm. of carbohydrate in the form of potato.

A glucose curve was also carried through with the following results, which are quite typical of those seen in nondiabetic cases of nephritis. There is a relatively slow rise to the maximum (0.241 per cent.), at one

TABLE 4.—RATE OF SUGAR EXCRETION FROM HOUR TO HOUR

March 7, 1921. Diet: Protein, 70 gm.; fat, 81 gm.; carbohydrate, 250 gm.

Time	Volume in C.c.	Spec. Gr.	Per Cent.	Gm.	Gm. per Hour
8 a. m. – 10 a. m.	116	1.022	0.71	0.82	0.41
10 a. m. – 12 m.	138	1.020	0.63	0.87	0.43
12 m. – 2 p. m.	152	1.021	0.66	1.00	0.50
2 p. m. – 4 p. m.	142	1.022	0.69	0.98	0.49
4 p. m. – 6 p. m.	170	1.020	0.56	0.95	0.47
6 p. m. – 8 p. m.	140	1.021	0.67	0.94	0.47
8 p. m. – 8 a. m.	775	1.019	0.55	4.26	0.36
Total...	1,633			9.82	

TABLE 5.—RESPONSE OF BLOOD AND URINE TO 100 GM. GLUCOSE

Time	Blood Sugar*	Urine					Remarks
		Vol., C.c.	Sp. Gr.	Per Cent.	Gm.	Gm. per Hr.	
9:00 a. m.	.....	95	1.019	0.35	....	....	100 gm. glucose
9:30 a. m.	0.092	...	.....	....	....	....	in 200 c.c. of
10:15 a. m.	0.208	...	.....	....	....	....	lemonade at
10:30 a. m.	.....	80	1.030	0.60	0.48	0.32	9:30 a. m.
11:00 a. m.	0.241	...	.....	....	....	....	
11:30 a. m.	0.151	88	1.016	0.91	0.80	0.80	*
12:30 p. m.	0.096	167	1.011	0.32	0.54	0.54	
2:30 p. m.	0.087	202	1.013	0.20	0.40	0.20	

* Folin, O., and Wu, H.[14]

and a half hours and the normal level is reached again in three hours. The specimen of urine passed before the ingestion of glucose showed that sugar passed through the kidney with a blood concentration in the vicinity of 0.092 per cent. A previous determination had shown a glycosuria of 0.11 per cent. with a fasting blood sugar of 0.068 per cent.; therefore, no question can be raised as to the extreme depression of the renal threshold.

In the course of ten months during which the glycosuria has been observed in hospital, there have been periods during which the patient

14. Folin, O., and Wu, H.: A System of Blood Analysis, Suppl. 1, J. Biol. Chem. **41**:367 (March) 1920.

has shown large changes in his body weight. A study of the fluid exchange and the rate of sugar excretion has shown no constant relation between the total fluid excreted and the amount of sugar in the urine. During one period there was a considerable fall in the sugar output with a retention of water, while during a subsequent period of diuresis the sugar showed no corresponding increase. This independence of sugar and fluid output has been noted in a majority of the published cases.

Case 3.—C. M., (metabolism No. 56), aged 74; bookkeeper.

History.—This man was admitted on account of a severe attack of scurvy occasioned by a deficient diet, the result of his financial straits. The sugar was found during the routine analysis of the urine. Subsequent questioning failed to reveal any of the usual symptoms or signs of diabetes mellitus. There was no thirst; no craving for sweets; no polyuria; no loss of weight. Nothing suggesting hyperthyroidism, and beyond a mild eczema of the hands, he had been very healthy. The family history was negative as regards metabolic disorders.

Physical Examination.—Temperature, 98 F.; pulse, 80; respiration, 20 (on admission). A well nourished man; who appears much younger than stated age. There is fluid in both knee joints, and the right olecranon bursa is filled with blood-stained fluid. There are intramuscular hemorrhages in the thighs and calves of both legs. The gums are much cut up where several teeth have been extracted recently on account of "pyorrhea" and are quite spongy around the remaining teeth. The pupils react to light and accommodation. The chest shows a moderate emphysema and bronchitis. The heart is slightly enlarged, there is an extrasystolic arrhythmia, the sounds are well heard, and there is a soft apical systolic murmur, poorly transmitted to the axilla. The vessel walls are definitely thickened. Blood Pressure: 160/84. The abdomen is negative, the genitalia are negative.

Urine: Acid; specific gravity, 1.021; albumin, faint trace; sugar, 2.5 per cent. Acetone and diacetic acid are absent. Microscopic examination shows a few leukocytes and occasional hyalin and granular casts.

Tests of Kidney Function,—Blood urea, 0.435 gm. per liter; uric acid, 5 mg. per hundred c.c.; creatinin, 1.64 mg. per hundred c.c.; plasma chlorid, 6.19 gm. per liter. The nephritic test diet gives a normal curve, and the phthalein excretion is 64 per cent. in two hours.

Blood: Erythrocytes, 4,900,000; leukocytes, 7,200; hemoglobin, 90 per cent. (Talquist). Wassermann test negative.

Diagnosis.—(1) Scurvy, (2) arteriosclerosis and arteriosclerotic kidney, (3) glycosuria.

Diary.—The scurvy cleared up rapidly with the ordinary anti-scorbutic foods, and the glycosuria was then studied. On ordinary diets with no limitation of carbohydrate he excreted from 33.2 to 53 gm. sugar daily, with a fasting blood sugar of 0.115 per cent., and a digestion sugar [15] of 0.133 per cent. Four days of a low calory diet (protein, 43 gm.; fat, 46 gm., carbohydrate, 29 gm.), followed by starvation for two days and three days of protein 40 gm., only sufficed to reduce the daily sugar excretion to 15.6 gm. The attempt to render the urine sugar free was then abandoned. On subsequent days, with a

15. Blood taken one and one-half hours after food.

gradually increasing diet, his output ranged from 20 to 57.5 gm. and the blood sugar from 0.112 to 0.129 per cent. when fasting, and from 0.121 to 0.161 per cent., one and half hours after food. In Table 6 a summary is presented of the diets, sugar excretion and blood sugars, fasting and digestion, during his first admission.

This table shows the independence of carbohydrate intake and output. The highest excretion being immediately after the starvation period, when the intake was at its lowest level. Allen [16] has directed attention to this apparent inability of the organism, be it normal or diabetic, to handle a sudden increase in the carbohydrate intake after a period of starvation or of low carbohydrate feeding. This also is

TABLE 6.—SUMMARY OF DIET, URINE AND BLOOD SUGAR OF C. M. (CASE 3)

Duration of Period	Diet			Urine Sugar		Blood Sugar	
	Protein	Fat	Carbohyd.	Per Cent.	Gm.	Fasting	Digestion
		House diet		2.2-3.8	32.2-52.4	0.115	0.133
5 days	0-40	0	0	0.6-1.3	16.0-23.1	0.138	0.144
12 days	90	131	90	1.0-3.1	20.3-57.5	0.112	0.141
8 days	100	150	100	1.2-1.7	22.3-38.1	0.116	0.161
5 days	100	125	150	0.8-1.6	28.7-39.0	0.117	0.121
4 days	101	125	200	1.6-1.7	25.3-48.8	0.114	0.126

TABLE 7.—REACTION OF SUGAR IN BLOOD AND URINE TO SPECIAL DIETS

Duration of Period	Diet			Urine Sugar		Blood Sugar*	
	Protein	Fat	Carbohyd.	Per Cent.	Gm.	Fasting	Digestion†
3 days		House diet		1.40-2.80	30.1-33.3	0.086	0.141
15 days	80	50	250	0.90-2.80	37.7-42.0	0.086	0.136
6 days	40-80	0	0	1.02-1.70	17.4-29.7	0.089	0.093
						0.046	0.061
3 days	0	100	0	0.92-2.01	13.3-16.1	0.078	0.087‡
4 days	80	80	250	1.60-5.40	37.5-54.0	0.089	0.242

* Blood sugars, Folin Wu method.
† Blood 1½ hours after food.
‡ Severe acidosis. Van Slyke 33.2 at end of third day, but rose to 60.5 volumes per cent. after two days of balanced diet.

shown in Table 7, where the sudden change from a pure fat diet to a liberal régime containing 250 gm. of carbohydrate is associated with a marked digestion hyperglycemia (0.212 per cent.) and one of the highest sugar outputs (54 gm.) ever found in this case. During the second admission studies were made of the effects of high carbohydrate, high protein and high fat intakes, with the following results.

After a preliminary period the patient was given a fixed diet for fifteen days with increasing fluid intakes of 1,000, 2,000, 3,000 and 4,000 c.c. per diem, but under these conditions the output showed only minor variations, an evidence of the lack of relation between the diuresis and the sugar leakage. With a pure protein dietary, there was a gradual drop in the blood sugar to the extremely low level of 0.046

16. Allen, F. M., and Associates: Three Cases of "Renal Glycosuria," Arch. Int. Med. **24**:523 (Nov.) 1919.

per cent., but even on this day he excreted 19.42 gm. sugar. So far there had been no sign of acidosis, but on the third day of a pure fat diet he developed an alarming acid intoxication. The bicarbonate reserve dropped to 33 volumes per cent., and he became drowsy. The diet was changed at once to a more varied one, and in two days all sign of the acidosis had disappeared (bicarbonate reserve 60.5 volumes per cent.)

Response to Added Glucose.—Three blood sugar curves were carried out, in each case the usual dose of 100 gm. was given in lemonade.

TABLE 8.—Response of Urine and Blood Sugar to 100 Gm. of Glucose

Hour June 16, 1920	Blood Sugar	Urine				Remarks
		Vol., C.c.	Per Cent.	Gm.	Gm. per Hr.	
8:45 a.m.	0.119	....	....	....	....	Test taken after two days of fasting and three of carbohydrate-free diet. 100 gm. glucose at 9:00 a.m.
9:00 a.m.	.....	....	2.60	....	....	
9:30 a.m.	0.200	....	....	....	....	
10:00 a.m.	0.200	85	2.17	1.85	1.85	
10:30 a.m.	0.204	....	....	....	....	
11:00 a.m.	0.200	125	3.03	3.78	3.78	
12:00 m.	0.188	120	4.50	5.40	5.40	
2:00 p.m.	0.150	125	4.50	5.62	2.81	
4:00 p.m.	0.138	125	2.70	3.37	1.18	
6:00 p.m.	0.150	120	2.50	3.00	1.50	
March 16, 1921						
8:45 a.m.	0.068	....	....	....	....	After two weeks of protein, 80 gm.; fat, 80 gm.; carbohydrate, 250 gm. 100 gm. glucose at 9:00 a.m.
9:00 a.m.	.....	80	1.50	....	....	
9:30 a.m.	0.122	....	....	....	....	
10:00 a.m.	0.136	134	2.07	2.77	2.77	
10:30 a.m.	0.178	....	....	....	....	
11:00 a.m.	0.170	72	2.60	1.87	1.87	
12:00 m.	0.063	166	2.40	3.98	3.98	
2:00 p.m.	0.061	126	1.40	1.76	0.88	
March 23, 1921						
8:45 a.m.	0.064	....	....	....	....	After three days protein, 40-80 gm.; carbohydrate free. 100 gm. glucose at 9:00 a.m. Voided at 10:15 a.m.
9:00 a.m.	.....	150	2.70	....	....	
9:30 a.m.	0.127	....	....	....	....	
10:00 a.m.	0.192	50	1.31	0.65	0.51	
10:30 a.m.	0.160	....	....	....	....	
11:00 a.m.	0.194	....	....	....	....	
12:00 m.	0.206	200	2.36	7.14	4.06	
2:00 p.m.	0.104	350	2.29	8.01	4.00	

The second curve is the one most nearly approaching normal. The maximum rise in blood sugar is a little high and its appearance is slightly delayed, but this can be accounted for by the arteriosclerosis and low grade nephritis [17] as shown by the albuminuria, casts, etc. The slow return to normal levels (three hours) can also be explained on the same grounds.

The first and third curves are decidedly abnormal, but are similar to those reported in other cases in which the test period was preceded by starvation or restricted carbohydrate intake. The fact remains, that in each case the kidney excretes sugar, while the glycemia is within normal limits, and in the third test the urine contained 2.7 per cent. sugar with a blood sugar of 0.064 per cent.

17. Janney, N.: Discussion, J. A. M. A. **75**:217 (July 24) 1920.

In this case the urine was collected in two hourly specimens during the day and a single specimen at night, and the hourly output was found to be remarkably constant. It was highest in the morning, fell during the afternoon and reached its lowest point during the night, showing in this regard a close resemblance to the output of albumin in that other anomaly of kidney action, orthostatic albuminuria.

TABLE 9.—RATE OF SUGAR EXCRETION FROM HOUR TO HOUR

March 7, 1921	Volume in C.c.	Specific Gravity	Sugar			Remarks
			Per Cent.	Gm.	Gm. per Hr.	
8-10 a.m.	95	1.034	4.59	4.36	2.18	Blood sugar: a. c., 0.104; p. c., 0.134
10-12 a.m.	150	1.030	2.86	4.29	2.15	
12- 2 p.m.	335	1.030	1.74	5.82	2.91	Diet: protein, 80 gm.; fat, 80 gm.; carbohydrate, 250 gm.
2- 4 p.m.	185	1.028	1.99	3.68	1.84	
4- 6 p.m.	155	1.029	2.02	3.13	1.57	
6- 8 p.m.	145	1.030	2.40	3.48	1.74	
8 p.m.-8 a.m.	1,050	1.021	1.36	14.28	1.19	
Total	2,115			39.05		

SUMMARY

Notes are presented on three cases of renal glycosuria. The first patient, after six years of observation, still presents a marked glycosuria without symptoms and with a normal amount of sugar in the blood. He is apparently in excellent health.

The second is a severe case of chronic diffuse nephritis, in which a glycosuria appeared while under observation. The glycosuria has been practically continuous since its onset twelve months ago. It is small in amount, the largest quantity being 16 gm.; it is largely independent of the carbohydrate intake, it required three days starvation before its disappearance, and reappeared on an intake of 30 gm. carbohydrate as green vegetables. The amount of glucose does not show any constant relation to the urinary volume. Synchronous sugar determination on blood and urine show the presence of a glycosuria with 0.068 per cent. sugar in the blood. The response to 100 gm. glucose falls within the limits of a nondiabetic case of nephritis. There are no other signs of a diabetes mellitus.

The third patient, aged 74, has a marked arteriosclerosis, (arteriosclerotic kidney), and was first seen on account of scurvy. The duration of the glycosuria is unknown. The glycosuria has been continuous for the past fifteen months, the usual output varying from 30 to 50 gm., and the ordinary changes in the diet had very little effect on the amount of sugar excreted. The sugar output was found to be independent of the urine volume. Synchronous studies of the blood and urine showed 2.7 per cent. sugar in the urine, with only 0.064 per cent. in the blood. The blood sugar curve following ingestion of 100 gm. glucose is somewhat atypical, but can be explained by the presence of arteriosclerosis and nephritis. There are no signs of diabetes mellitus.

It is generally recognized that there are two types of renal glycosuria [17]: the one of unknown or idiopathic origin in which the blood sugar curve is of a strictly normal order, the other, is associated with a chronic diffuse nephritis or an arteriosclerosis, in which case the patient shows a remarkably high and prolonged rise in the blood sugar, which is probably a retention phenomenon, or may be connected with the high diastatic activity of the blood, so often seen in severe nephritis. The first case is an example of the idiopathic type, while the second and third are examples of the second group.

Acknowledgment is due to Dr. E. H. Mason who has kindly placed at my disposal much of the data connected with the second and third cases; also to Miss Lane for technical assistance.

CHEMICAL STUDIES OF THE BLOOD AND URINE OF SYPHILITIC PATIENTS UNDER ARSPHENAMIN TREATMENT

WITH A NOTE ON THE MECHANISM OF EARLY ARSPHENAMIN REACTIONS *

CHARLES WEISS, PH.D., AND ANNA CORSON, B.Sc.
PHILADELPHIA

The chemical analyses of the blood and urine of five cases of tertiary syphilis form part of an investigation conducted in collaboration with Schamberg, Kolmer and Raiziss [1] on the subject of the causes and mechanism of the severe reactions occasionally observed after the intravenous administration of alkaline solutions of arsphenamin. Since the clinical and pathological literature on arsphenamin reactions has frequently been reviewed, we will concern ourselves here with a small number of available papers that deal with strictly chemical investigations made by modern acceptable methods.

REVIEW OF THE LITERATURE

Very little literature is available concerning the effects of arsphenamin on metabolic processes. Marischler and Schneider,[2] who were among the first to investigate this problem, unfortunately used the subcutaneous route of administration. Since the journal in which their paper is published is inaccessible, a brief summary of their work will be of interest. They investigated three cases of syphilis: one primary, one secondary and one tertiary. The patients were kept on a constant diet. An increased excretion of calcium oxid and phosphorus in the urine and feces was found in all three cases, and in one case there was an increase in the phosphorus to nitrogen ratio, with a correspond-

* From the Dermatological Research Institute.
* Investigation aided by funds accruing from the preparation of arsphenamin.
* A preliminary note on this subject was published in the Proceedings of the Society for Experimental Biology and Medicine **18**:210, 1921.

1. Schamberg, J. F.; Kolmer, J. A., and Raiziss, G. W.: Experimental and Clinical Studies of the Toxicity of Dioxydiamino-Arsenobenzol Dihydrochloride, J. Cutan. Dis. **35**:286, 1917. Schamberg, J. F.; Kolmer, J. A.; Raiziss, G. W., and Weiss, C.: Laboratory and Clinical Studies Bearing on the Causes of the Reactions Following Intravenous Injections of Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **1**:235, 1920. Weiss, C.: Phenol Elimination in the Dog After Intravenous Injection of Neo-Arsphenamin, Proc. Soc. Exper. Biol. & Med. **17**:103, 1920.

2. Marischler, J., and Schneider, N.: The Effect of Subcutaneous Injections of Salvarsan on Metabolism, Lwowski Tygodnik Lekarski (Lemberg Medical Weekly [Polish]) **7**:63, 81, 1912.

ing decrease in the nitrogen output. These authors probably used acid solutions of arsphenamin (although no data as to this are given in the original article). They concluded that arsphenamin acts like an acid, combining with the alkali of the body, especially with the calcium of the bone cells.

Rowntree, Marshall and Chesney [3] reported a case of "tabes dorsalis with acute and chronic nephritis" in which death resulted from arsphenamin poisoning. The total nonprotein and amino-nitrogen of the blood were distinctly above normal, being 150 and 12.4 mg. per hundred c.c., respectively.

Rappleye [4] studied the effects of intravenous injections of arsphenamin on the blood urea and the phenolsulphonephthalein elimination in paretic patients. In one series of cases, with normal urea values just before injection (from 7.8 to 15.4 mg. urea nitrogen per hundred c.c. of blood), only three out of the nine patients who were examined one hour after the injection, showed very small increases of from 2.5 to 3.1 mg. urea nitrogen in 100 c.c. of blood. In two other series of cases tested three and twenty-four hours after injection, respectively, no changes were detected.

Rappleye also tested the blood urea and kidney function in another series of cases which had been under treatment for a long time, and had received a total of from 11 to 32 gm. of diarsenol (the Canadian brand of arsphenamin). Only two of the four patients who had received more than 19 gm. of diarsenol showed low dye elimination (10 and 20 per cent., respectively). Although these patients "were in bed and suffering from considerable edema and were in poor general condition, showing occasional hyalin and granular casts in the urine," their blood urea nitrogen values were normal. Of the remaining six patients who had received less than 19 gm. of diarsenol, all had normal blood urea nitrogen values, although five of them eliminated low percentages of phenolsulphonephthalein (from 20 to 50 per cent.), and three of the latter showed albumin and casts in the urine. In only three of the entire series of ten cases, were the phenolsulphonephthalein and urea-nitrogen values comparable. These three gave normal figures. In all others, the phenolsulphonephthalein elimination was much lower than normal, but there was no increase in the urea nitrogen of the blood. Rappleye concludes that diarsenol has no deleterious effect on the kidneys when their function is good at the outset.

---

3. Rowntree, L. B.; Marshall, E. K., and Chesney, A. M.: Studies in Liver Function, Tr. Assn. Am. Phys. **29**:586, 1914.

4. Rappleye, W. C.: Notes on the Effect of Intravenous Diarsenol, J. Lab & Clin. M. **4**:630, 1919.

Elliott and Todd [5] made similar studies on syphilitic young men who were receiving weekly intravenous injections of arsphenamin. They report as follows: Of twenty patients on whom phenolsulphonephthalein determinations were made both before and after a course of six arsphenamin injections with a total dosage of 2.7 gm., five showed a reduction of from 10 to 17 per cent. each, while the other fifteen remained practically unchanged. The urea-nitrogen content of the blood in these twenty cases showed an average of 14.3 mg. per hundred c.c. before and 16.0 mg. after treatment, or practically no change. One case showed an increase of 9 mg. No details are given of these analyses.

In another series of nine cases, receiving injections twice a week with the same total dosage (2.7 gm.), the results were as follows: Before injection, the urea nitrogen of the blood was normal, varying from 12.6 to 20 mg. per hundred c.c. of blood. After injection, it increased slightly (2 mg. per hundred c.c.) in four of the patients, but none of them had more than 20 mg. urea-nitrogen per hundred c.c. (the upper normal limit). The phenolsulphonephthalein elimination, on the other hand, was low to begin with—from 41 to 58 per cent. before injection—and was decreased somewhat, being from 40 to 51 per cent. after injection. In three of these cases there were reductions of from 11 to 17 per cent., while in two others there was 5 per cent. reduction, without corresponding retention of nitrogen.

In one case of acute syphilitic nephritis, Elliott and Todd observed high blood urea figures which declined rapidly under the arsphenamin treatment. Albumin also disappeared from the urine. The phenolsulphonephthalein excretion, on the other hand, which was rather high to begin with, declined somewhat during the treatment, in spite of the obvious renal improvement. The authors concluded that "these findings suggest that the admitted inadequacy of the phenolsulphonephthalein test to detect acute nephritis applies also to syphilitic nephritis."

Bailey and MacKay,[6] in an extensive chemical study of the blood and urine of twenty-five cases of syphilis in which toxic jaundice had developed under combined mercury and novarsenobillon (French brand of neo-arsphenamin) treatment, observed:

(1) In eleven of the cases, bile pigments were found in the plasma, and, as a rule, also bile salts.

(2) The greatest excretion of urobilinogen and urobilin was in the jaundiced cases. In the absence of jaundice, the output of these pigments was less than half.

---

5. Elliott, J. A., and Todd, L. C.: Effects of Arsphenamin on Renal Function in Syphilitic Patients, Arch. Dermat. & Syph. **2**:699, 1920.

6. Bailey, C. V., and MacKay, A.: Toxic Jaundice in Patients Under Antisyphilitic Treatment, Arch. Int. Med. **25**:628 (May) 1920.

(3) In the voided urine, the relative excretion of urobilinogen to urobilin was greatest in the well patients and least in the severe liver cases, indicating a decreased excretion of oxidase in the latter.

(4) In twelve of the patients with no disorder of the liver, the percentage of cholesterol varied from 0.117 to 0.210, with an average of 0.155, or within a fairly normal range. In all of the twenty-five cases of toxic jaundice, the cholesterol value was strikingly high, varying from 0.165 to 0.292 per cent., with an average of 0.235 per cent. In twenty-one of the twenty-five cases the values were over 0.2 per cent. Bailey and MacKay consider hypercholesteremia as being an early and marked sign of toxic jaundice and a valuable indication of a precarious state of the liver in this disease.

(5) The blood sugar and rate of excretion of sugar in the urine were normal in all of these patients.

(6) As for the nitrogenous constituents of the blood of these patients (who were on a high protein diet), the urea-nitrogen was normal (from 8 to 20 mg. per hundred c.c. of blood) in eight, but above normal (22 mg. and above) in the majority; one was as high as 49 mg. per hundred c.c. of blood. These abnormal values were ascribed, in part, to the high protein diet and the various physic restrictions placed on the patients (soldiers), and, in part, to impaired kidney elimination, since they were accompanied by slight increases in the creatinin and marked increases in the uric acid of the blood as well as a decreased elimination of uric acid in the urine. The high blood uric acid was attributed to an increased production of this substance resulting from a destruction of liver nuclear substance. It is of interest to note that casts and protein were found only occasionally in the urines of a few of those patients who showed retention of nitrogen in the blood.

While this manuscript was being prepared, Anderson's paper on the effect of arsphenamin on kidney function appeared.[7] This author reports chemical analyses of the blood in thirty-eight cases of syphilis in which the total dosage of arsphenamin ranged from 8 to 21 gm. with an average of about 14 gm. The treatment extended over a period of two years and included inunctions or injections of various mercurials in addition to arsphenamin injections. Of the thirty-eight patients (we omit here the case which he characterized as nephropathic), twenty-four had total nonprotein nitrogen values higher than 30 mg. (the upper normal limit), four of these ranging from 40 to 46 mg. per c.c. of blood. The urea-nitrogen and creatinin values were normal in all, although one case showed albumin and globulin in the urine

7. Anderson, H. B.: Some Observations on the Use of Arsphenamin, Am. J. M. Sc. **162**:80, 1921.

(no casts). The phenolsulphonephthalein test gave the following results. Of five patients with somewhat subnormal dye elimination (from 45 to 50 per cent. in two hours) only one patient had a nonprotein nitrogen value of 46, the others being normal. Case 25 of Anderson, diagnosticated as "tabes and nephritis" had a phenolsulphonephthalein elimination of 40 per cent. in two hours, total nonprotein nitrogen 37 mg. per hundred c.c. of blood, and urea and creatinin normal. The urine showed a distinct trace of albumin but no globulin and a few granular casts. Anderson draws the conclusion that there is no evidence of kidney injury.

In this connection, some of the recent histopathologic studies of Kolmer and Lucke [8] must be referred to briefly. These authors found the following changes in normal rabbits and rats injected intravenously with repeated small (therapeutic) doses of either neo-arsphenamin or alkaline arsphenamin:

> The liver showed small areas of focal necrosis and slight periportal fibrosis. The latter was confined to the tissue about the bile ducts and blood vessels. The kidneys revealed vascular and tubular changes characterized as "nephrosis." More or less marked chronic passive congestion was found with moderate hemosiderosis in the spleen; inconspicuous amounts of hemosiderin occurred in the lung. Occasional vessels contained thrombi composed of partly or entirely conglutinated or hyalinized erythrocytes. The lipoids of the suprarenals were at first increased in quantity; later a slight exhaustion appeared. Parenchymatous changes of mild degree were seen in the various organs.

PLAN AND METHODS OF INVESTIGATION

As has been brought out in the review of the literature, previous writers have limited their work to a single chemical analysis of the blood and urine of the patient after a course of arsphenamin injections had been given, with the hope of detecting kidney injury. The present work was begun before any of the above publications had appeared. Our object being primarily to study the mechanism of early arsphenamin reactions, we deemed it necessary to hospitalize our cases, and to make frequent analyses of the blood and urine before injection and then for a sufficient interval after treatment. In this way we hoped to detect changes, which could, with some degree of certainty, be ascribed to the action of the drug.

Five cases of tertiary syphilis with varying degrees of optic atrophy were selected from the Skin Clinic of Dr. Jay F. Schamberg, Polyclinic Hospital, Graduate School of Medicine, University of Pennsylvania. They were kept in a ward at the Polyclinic Hospital and given the usual house diet, which was low in proteins and fats, rich in carbohydrates and fairly constant from day to day. Their water intake

8. Kolmer, J. A., and Lucke, B.: Experimental Studies on the Histopathologic Changes Produced by Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **2**:289, 1920; Ibid. **3**:483, 1921.

was also controlled. Blood specimens were taken in the first two cases, three hours after a constant prescribed breakfast and in the last three cases, before breakfast.

The following were investigated: (1) The urea and total nonprotein nitrogen, sugar and uric acid of the blood, by the methods of Folin and Wu.[9] The total nonprotein nitrogen was estimated by the digestion and direct nesslerization technic, and urea nitrogen by the acration and titration method of Van Slyke and Cullen.[10] (2) The carbon dioxid combining power of the plasma was determined by Van Slyke's method.[11] (3) Kidney function was determined by the phenolsulphonephthalein test of Rowntree and Geraghty,[12] the dye being injected intramuscularly. (4) The daily twenty-four hour specimens of urine were also analyzed routinely for sugar and albumin, and microscopic examinations were made of the sediment. (5) The hydrogen-ion concentration of the blood and urine was measured by the colorimetric method of Sörenson, as developed by Bayliss[13] and Clark,[14] respectively. (6) Total nitrogen in the daily twenty-four-hour urine was estimated by the gross Kjeldahl method in the usual way. (7) Arsenic elimination in the urine was determined by Green's microtitration method. These results are reported separately.[15]

Before beginning this investigation the various methods employed were carefully tested out by running "recovery" and "control" experiments. All determinations reported were done in duplicate, and only checking results were accepted.

REPORT OF CASES[16]

Case 1.—T. M., aged 38; optic atrophy of left eye. This patient was in good physical condition. He had been under continuous treatment for more than two years, and had always suffered reactions. During the "control periods" (before injection), normal values for urea, total nonprotein nitrogen and blood sugar were observed. Oct. 26, 1920, before breakfast, the patient was given an intravenous injection of 0.6 gm. of an alkaline solution of arsphenamin, dissolved in 120 c.c. distilled water. The patient had a very mild reaction—nausea and vomiting, which continued until the next morning. Three hours

9. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919; Ibid. **41**:367, 1920.

10. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211, 1914.

11. Van Slyke, D. D.: A Method for the Determination of Carbon Dioxid and Carbonates in Solution, J. Biol. Chem. **30**:347, 1917.

12. Rowntree, L. G., and Geraghty, T. J.: Described by Myers," pp. 103-104.

13. Bayliss, W. M.: The Neutrality of the Blood, Brit. J. Physiol. **53**: 162, 1919.

14. Clark, W. M.: The Determination of Hydrogen Ions, Williams and Wilkins Co., Baltimore, 1920.

15. Weiss, C., and Raiziss, G. W.: The Elimination of Arsenic in the Urine of Syphilitic Patients After Intravenous Injection of Arsphenamin, Arch. Int. Med. (1922) to be published.

16. Additional data are given in the preceding paper.[15]

after the injection, the total nonprotein nitrogen rose to 32.9 mg., which is slightly above the upper normal limits given by Myers.[17] The urea remained unchanged. No food had been taken during this interval. The blood sugar increased from 100 to 123.8 mg. per hundred c.c. On the following morning, the figures for urea and total nonprotein nitrogen (blood specimen obtained three hours after a prescribed breakfast) continued to rise, the former reaching 6.8 mg. above the normal range.

TABLE 1.—Showing Chemical Changes in the Blood of Syphilitics During Arsphenamin Treatment

Date	Total Nonprotein Nitrogen *	Urea Nitrogen	Sugar	Remarks
Case 1: T. M.; male; aged 38; optic atrophy				
10/25/20	24.2	11.1	85.1	
10/26/20	30.0	13.2	100.0	†
10/26/20	32.9	13.2	123.8	V‡
10/27/20	36.8	20.6	130.2	V
10/29/20	31.4	17.3	133.8	
11/ 2/20	39.5	14.3	115.6	
11/ 4/20	33.4	14.9	108.9	
11/ 8/20	34.3	22.4	131.6	
11/ 9/20	23.2	8.1	133.3	†
11/ 9/20	38.4	9.4	129.9	D‡
11/10/20	44.3	14.8	121.2	
11/13/20	34.5	11.3	137.9	
11/16/20	32.6	12.6	137.9	
11/18/20	31.0	12.4	139.9	
11/22/20	32.4	18.1	121.6	
11/23/20	34.8	16.9	116.3	V†
11/24/20	38.2	18.3	117.6	
11/26/20	30.3	13.5	108.1	
Case 2: M. J. male; aged 28; optic atrophy				
1/19/21	32.5	11.4	98.5	
1/20/21	32.1	11.4	88.3	
1/21/21	32.6	11.7	111.4	
1/25/21	30.7	12.2	75.5	†
1/25/21	32.5	15.5	158.8	V‡
1/27/21	31.5	11.3	113.0	
1/28/21	31.5	12.6	89.9	
1/31/21	30.7	14.2	137.9	
2/ 2/21	38.8	18.6	96.4	G
2/ 4/21	35.8	17.5	119.0	
2/ 7/21	30.9	14.3	107.5	

* All figures are given in milligrams per hundred c.c. of blood.
† Injection immediately after sample was drawn.
‡ Patient received an intravenous injection of 0.6 gm. arsphenamin three hours before this sample of blood was drawn.
V = "reaction"—patient vomited.
D = severe reaction with vomiting, diarrhea and pain in the legs.
G = gastric crisis. C = slight reaction, chills.

During the succeeding days, the values fluctuated somewhat. One week after injection a total nonprotein nitrogen value of 39.5 mg. per hundred c.c. of blood was observed. The urea nitrogen of this specimen was normal (14.3 mg.). The highest urea value, observed thirteen days after injection, was 22.4 mg. with a corresponding nonprotein nitrogen figure of 34.28 mg., both indicative of a very mild nitrogen retention.

After the second injection, the reaction was much more severe. The patient became very sick; he had vomiting, diarrhea, pain in the legs and oliguria with bile tinged urine. The blood specimen taken three hours after this injection (no food having been consumed) showed increases similar to those seen after the first dose. On the next morning, however, the highest value

17. Myers, V. C.: Practical Chemical Analysis of Blood, St. Louis, C. V. Mosby Co., 1921, pp. 70-82, 103-104.

for total nonprotein nitrogen was obtained, 44.3 mg. per hundred c.c. blood. The urea-nitrogen remained normal, 14.8 mg. per hundred c.c. An increase of 2 gm. above the usual range was observed in the urinary nitrogen excretion of the succeeding day. The urea and sugar continued to remain normal during the next two weeks, but the total nonprotein nitrogen figures were slightly above normal.

The third injection, now given, was followed by a mild reaction, and the analytical figures were very much similar to those seen after the first dose. The blood sugar values never assumed pathologic significance.

Case 2.—J. M., male, aged 28; total optic atrophy. This patient was in good physical condition; he had been under continuous treatment for over two years. During the control period (one week) the values for urea and total nonprotein nitrogen were or gradually became normal. A mild reaction (vomiting) followed the first injection of 0.6 gm. of alkaline arsphenamin. The blood specimen taken three hours after this injection (the patient having taken no food) showed slight rises (from 2 to 3 mg.) in the urea and total nonprotein nitrogen. The blood sugar was more than doubled but never assumed pathologic significance. No other significant changes were observed until eight days later when the urea and total nonprotein nitrogen rose above their usual values, reaching 18.6 and 38.8 mg. per hundred c.c. of blood, respectively. Both gradually declined during the course of the next few days.

Case 3.—K. W., male, aged 39; locomotor ataxia; total optic atrophy. This patient was not in good nervous or physical condition. During the control period of observation (lasting twelve days) the values for urea-nitrogen, sugar and uric acid were normal. The total nonprotein nitrogen values, however,

TABLE 2.—Biochemical Data on Case 3

K. W.; male; aged 39; optic atrophy

Date	Total Nonprotein Nitrogen*	Urea Nitrogen	Sugar	Uric Acid	Remarks
2/23/21	32.2	9.9	126.6		
2/25/21	33.8	11.0	124.6		
2/28/21	35.1	12.5	132.5	2.4	
3/ 2/21	35.2	12.3	128.2	2.4	
3/ 4/21	33.0	13.7	144.4	2.4	
3/ 7/21	28.0	9.1	173.2	1.3	†
3/ 7/21	30.9	14.5	160.6	1.4	C‡
3/ 8/21	31.4	11.7	173.5		
3/10/21	28.9	8.6	160.6	2.4	
3/14/21	29.1	6.0	95.5	2.4	
3/16/21	27.9	9.6	96.4	2.4	
3/18/21	24.0	7.3	98.0		
3/21/21	26.5	12.2	86.4	2.4	†
3/21/21	29.0	14.0	149.2	2.4	V‡
3/22/21	35.2	14.9	147.6	2.0	
3/24/21	24.6	8.9	107.0	...	†
3/24/21	26.4	10.3	100.5	...	C‡
3/25/21	26.5	13.1	102.6		
3/29/21	22.9	7.3	97.3	2.5	
3/31/21	24.9	10.0	98.2	2.4	
4/ 5/21	34.7	11.2	95.2	2.6	
4/ 7/21	26.1	14.9	91.3	2.2	

* All figures are given in milligrams per hundred c.c. of blood.
† Injection immediately after sample was drawn.
‡ Patient received an intravenous injection of 0.6 gm. arsphenamin three hours before this sample of blood was drawn.
V = "reaction"—patient had severe chills.
C = slight reaction—chills.

were often somewhat above normal, ranging from 28 to 35.2 mg. per hundred c.c. of blood. The first injection of 0.6 gm. arsphenamin was not followed by any untoward symptoms, except slight chills. The usual small increases in the urea and nonprotein nitrogen (and uric acid) of the blood were observed three hours after the injection. No other significant changes were detected.

The second injection of 0.6 gm., given a fortnight after the first, was followed by somewhat more severe chills. The blood findings were similar, except that the blood sugar rose appreciably three hours after the injection.

Three days later a third injection was given and was followed by similar results. The urea nitrogen content of the blood in this patient never rose above 15 mg. per hundred c.c.

CASE 4.—G. R., male, aged 48; partial optic atrophy; diminished hearing; tremor; Rhomberg positive. Loss of tactile sensation. General physical condition fair. In this case and in Case 5 an effort was made to determine whether or not the alkali used to neutralize arsphenamin produced any appreciable change in the carbon dioxid combining power of the plasma or in the hydrogen-ion concentration (p_H) of the blood or urine. In addition to chemical analyses of the blood,[18] we made phenolsulphonephthalein elimination tests and careful examination of the urine for albumin and casts.

During the control period of observation (one week) this patient showed abnormal values for urea and total nonprotein nitrogen of the blood, from 24 to 30 and from 36 to 41 mg. per hundred c.c., respectively. The carbon dioxid and sugar values were, however, normal. The phenolsulphonephthalein elimination was not comparable with the nitrogen figures, being within the normal range. The urine frequently showed a few granular and hyalin casts, renal cells and leukocytes and an occasional red blood cell. There was no proteinuria or glycosuria. The p_H of the urine was within normal range.

After the first injection of 0.6 gm. alkaline arsphenamin no untoward symptoms were observed. There were the usual small increases in the total nonprotein nitrogen and sugar of the blood three hours after the injection. The urea, carbon dioxid combining power and the p_H of the blood remained unchanged. The urine taken immediately after the injection was completed, showed a very small increase in alaklinity. Forty-four hours after the injection an appreciable increase in the urea and total nonprotein nitrogen of the blood was observed. The former rose to 32.3 mg. and the latter to 44.1 mg. per hundred c.c. blood. One week later a second injection of 0.6 gm. was given. There was no clinical reaction. The increase in total nonprotein nitrogen observed three hours after the injection was 4 mg. per hundred c.c.; the small increases in urea nitrogen and sugar of the blood were similar to those usually noted. There was no increase in the p_H of the blood. A specimen of urine, taken immediately after the injection was completed, showed a very small increase in alkalinity similar to that noted in the first injection. Two days after the injection the urea dropped to normal although the total non-protein nitrogen remained unchanged. At no time was any decrease in the phenolsulphonephthalein elimination observed.

CASE 5.—C. J., male, aged 53; partial optic atrophy. General physical condition very good; patient complained of headche and occasional pain in lumbar region.

This patient showed abnormal total nonprotein nitrogen content of the blood, although the urea and carbon dioxid combining power were normal. He never showed any reaction (except very mild diarrhea) nor any subnormal phenolsulphonephthalein elimination, although he regularly eliminated a few hyalin and granular casts, leukocytes and red cells in the urine. The second injection of 0.6 gm. alkaline arsphenamin (which we were able to follow more carefully than the first) resulted in no appreciable change, other than the usual marked rise in blood sugar (observed three hours after the injection). The carbon dioxid combining power of the plasma remained unaltered.

The third injection showed a more appreciable rise in the total nonprotein (but not in urea) nitrogen, and a similar increase in blood sugar three hours after the injection.

---

18. Specimens of blood were taken before breakfast.

TABLE 3.—Biochemical Data on Cases 4 and 5

Case 4: G. R.; male; aged 48; optic atrophy

Date	Blood Analyses				Kidney Function Tests				Remarks
	Total Nonprotein Nitrogen*	Urea Nitrogen	Sugar	Plasma† CO_2	Phenolsulphonephthalein Elimination, per Cent.		Albumin	Sediment	
					First Hour	Total 2 Hrs.			
6/15/21	41.1	24.0	88.9	58	55	70	Negative	One of two granular casts, slight amount of sediment	
6/17/21	41.1	30.0	109.8	58	50	65	Negative	Many granular casts, few hyalin casts, occasional red blood cells, many white blood cells	
6/20/21	36.5	23.9	101.8	58	45	60-65	Negative	Many granular and hyalin casts, few renal cells and white blood cells	
6/22/21	36.1	29.6	105.3	63	..	..	Negative	Few casts and white blood cells	‡
6/22/21	38.1	28.3	122.7	63	..	..	.....	.....	§
6/24/21	44.1	32.3	90.5	58	..	..	Negative	Few casts, many white blood cells	
6/28/21	35.5	21.4	102.0	60	50	±60	Negative	Few casts and white blood cells	‡
6/28/21	39.5	23.3	115.3	60	..	..	.....	.....	§
6/30/21	39.2	19.6	92.0	55	50	65-70	Negative	Increase in amount of sediment, many casts, white blood cells, few epithelial cells	

Case 5: S. J.; male; aged 58; optic atrophy

7/ 7/21	36.7	20.3	.....	58	..	..	.....	.....	‡
7/ 7/21	....	....	.....	58	..	..	.....	.....	§
7/12/21	33.1	15.4	117.3	57	45	65	Negative	Slight amount of sediment, occasional casts, red blood cells, white blood cells	
7/14/21	34.9	19.2	137.9	57	50	60	Negative		
7/18/21	34.2	12.3	91.3	55	..	..	Negative	Few granular casts, white blood cells, renal cells, and spermatozoa	‡
7/18/21	35.1	12.3	137.9	56	..	..	.....	.....	D¶
7/21/21	32.0	15.9	97.1	56	50	60-65	Negative	Occasional hyalin cast and white blood cells	
7/25/21	33.3	12.8	94.8	61	..	..	Negative	Occasional granular cast and white blood cells	‡
7/25/21	38.2	12.9	120.9	..	..	..	.....	.....	§
7/28/21	30.6	17.4	109.1	53	40-45	65	Negative	Occasional white blood cells and a few spermatazoa	

* All figures for total nonprotein nitrogen, urea nitrogen and sugar are given in milligrams per hundred c.c. of blood.

† Cubic centimeters of carbon dioxid reduced to oxygen, 760 mm. bound as bicarbonate by 100 c.c. of plasma.

‡ Injected immediately after sample of blood was drawn.

§ Patient received an intravenous injection of 0.6 gm. arsphenamin three hours before this sample of blood was drawn.

¶ Blood drawn during injection after three fourths of dose had been administered.

± This phenolsulphonephthalein test was made the afternoon prior to injection.

D = very mild diarrhea.

THE MECHANISM OF EARLY ARSPHENAMIN REACTIONS

Evidence has been brought forth in the review of the literature as well as from our own data, that: (a) arsphenamin does not exert any selective injurious action on the kidneys; (b) patients with injured kidneys do not necessarily manifest arsphenamin reactions; and (c) patients with good kidney function may suffer from severe reactions.

What, then, is the mechanism of arsphenamin reactions?

Numerous theories have already been suggested and these have been reviewed by one of us (C.W.[1]) as well as by Hirano.[19] The latter suggested the hypothesis that arsphenamin causes a diminution in the epinephrin content of the suprarenals and, therefore, of the circulating blood thus producing shock to the organism. Work done in this Institute by Drs. Lucké, McCouch and Kolmer (*Journal Pharmacol. Exp. Therapeutics,* 1922 [in press]) casts very grave doubt on Hirano's findings and interpretation. That arsphenamin reactions bear no relation to true anaphylactic shock has been shown by the pharmacologic studies of Hanzlik and Karsner.[20]

These authors, as well as Jackson and Smith,[21] have shown that in experimental animals, even therapeutic doses of arsphenamin raise the pulmonary arterial pressure and dilate the right heart. Hanzlik and Karsner maintain that the symptoms observed after arsphenamin or neo-arsphenamin injections are due primarily to injury to the circulatory apparatus caused by the arsenic. (No distinction is to be drawn between inorganic and organic arsenicals in their opinion.) "Amelioration or partial protection afforded by adrenalin or atropin is due entirely to improvement in the circulation."

Injury to the circulatory apparatus (and, perhaps, also destruction of erythrocytes due to the hemolytic action of arsphenamin) probably accounts for the small but constant increases in total nonprotein nitrogen of the blood observed by us within three hours after injection.

The recent toxicological data of Willcox and Webster [22] showing the wide-spread distribution of arsenic in the organs of fatal cases of

19. Hirano, N.: Experimental Studies on the Nature of Anaphylactoid Reactions Caused by the Repeated Intravenous Injection of Salvarsan, Kitasato Arch. Exper. M. **3**:1, 1919.

20. Hanzlik, P. J., and Karsner, H. T.: A Comparison of the Prophylactic Effects of Atropin and Epinephrin in Anaphylactic Shock and Anaphylactoid Phenomena from Various Colloids and Arepsenamin, J. Pharmacol. & Exper. Therap. **14**:425, 1920. Effects of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Bronchi of Perfused Lungs, loc. cit. **14**: 449, 1920.

21. Jackson, D. E., and Smith, M. I.: An Experimental Investigation of the Cause of Early Death from Arsphenamin, J. Pharmacol. & Exper. Therap. **12**:221, 1918.

22. Willcox, W. H., and Webster, J.: The Toxicology of Salvarsan, Brit. M. J. **1**:473, 1916; The Analyst **41**:231, 1916.

arsphenamin intoxication, as well as the histopathological studies of Kolmer and Lucké [8] already alluded to (showing that practically very organ is to a mild degree deleteriously affected during a course of arsphenamin injections in experimental animals), lead us to suggest that early arsphenamin reactions may not be due primarily to injury to any specific organ alone but to a general tissue injury which may be ascribed to the toxic action exerted by the drug or the products of its oxidation or reduction in the tissues of certain hypersensitive cases. That the liver also suffers injury is suggested by comparing our observation of increases in total nonprotein nitrogen, without corresponding increases in urea-nitrogen of the blood, with similar data published by Losee and Van Slyke [23] and Killian [24] on eclampsia, and of Rowntree, Marshall and Chesney [3] in various other diseases in which the liver is known to be involved.

SUMMARY

Five cases of tertiary syphilis with varying degrees of optic atrophy were studied. The details of the chemical analyses of the blood and urine and the history of the cases will be found in Tables 1, 2 and 3 and in the text. Herewith are presented a brief summary of the essential points noted.

1. *Urea and Total Nonprotein Nitrogen of the Blood.*—(a) Small but definite increases in the nonprotein nitrogen of the blood (from 2 to 5 mg. per hundred c.c.) were observed three hours after practically every intravenous injection of 0.6 gm. doses of arsphenamin (ten out of twelve injections). These increases cannot be accounted for by the nitrogen content of arsphenamin (which is 5 per cent.). The maximum rise accompanied the severest reaction (Case 1). The increases in urea nitrogen were not always parallel to those in the nonprotein nitrogen and often were absent or exceeded them.

(b) Blood specimens examined at intervals after every injection of arsphenamin showed significant increases above the original limits, only in those cases (Cases 1 and 2), in which the reactions were most pronounced. The nonprotein nitrogen in Case 1, which was from 24 to 30 mg. before injection, rose twenty-four hours after the injection to 44 mg. per hundred c.c. of blood. Case 2, with a less severe reaction, showed a milder increase (from 33.5 before, to 38.8 mg. eight days after injection). The urea nitrogen figures, however, remained normal.

(c) In no case was the final total nonprotein nitrogen or urea-nitrogen of the patient, when discharged (after one, two or three 0.6

23. Losee, J. R., and Van Slyke, D. D.: The Toxemias of Pregnancy, Am. J. M. Sc. **153**:94, 1917.
24. Killian, H.: Proc. New York Path. Soc., February, 1921.

gm. doses of arsphenamin) any higher than when admitted. On the contrary, many reductions were noted. All of the patients benefited greatly by the low protein diet and hospital care, as well as by the injections.

(d) Of the five cases studied(one (Case 4) had urea and total nonprotein nitrogen values distinctly above normal before treatment was begun. Yet this patient never showed untoward symptoms. On the other hand, Case 1, with normal blood figures, reacted severely. We cannot, therefore, in every case, ascribe arsphenamin reactions to impaired kidney function alone, as suggested by Wechselmann.[25]

2. *Blood Sugar.*—Marked but not pathologic increases in blood sugar occurred fairly constantly three hours after injection. Two or three times (Cases 2 and 3) we noted that the blood sugars were doubled, although no food had been taken during this interval. As a rule, these increased values gradually subsided in the course of a few days. Whether these sudden increases were due to stimulation of the suprarenals, resulting from the action of the drug or from mere fright, is a matter to be investigated.

Marked variations in blood sugar were also noted from day to day in specimens taken at the same hour before breakfast. The nervous state of the patient and the weather conditions seemed to be controlling factors.

3. *Uric Acid.*—The uric acid of the blood was studied in Case 3 and it was found to be constantly normal during the investigation.

4. *Carbon Dioxid Combining Power of Plasma.*—In cases 4 and 5 normal values were observed both before and during treatment. The amount of alkali added to acid arsphenamin to produce the disodium salt was insufficient to change either the bicarbonate reserve or the hydrogen ion concentration of the plasma or of the urine. Ferannini [26] draws similar conclusions from his pharmacologic studies of the respiratory rate in dogs.

5. *Phenolsulphonephthalein Elimination.*—The elimination of this dye was normal in each of the two patients studied (Cases 4 and 5) although the former showed distinct signs of nephritis. There were no changes after arsphenamin treatment.

The writers wish to thank Dr. Jay F. Schamberg, Dr. John A. Kolmer and Dr. George W. Raiziss of this Institute for their kind cooperation throughout the work.

25. Wechselmann, W.: Ueber die Pathogenese der Salvarsantodesfälle, Berlin, Urban and Schwarzenberg, 1913.

26. Ferrannini, L.: Richerche Sperimentali sull' azione farmacologia del Salvarsan, Riforma med. **27**:1065-1068, 1101-1106, 1126-1128, 1911.

STUDIES IN THE VARIATION OF THE LENGTH OF THE Q-R-S-T INTERVAL *

G. K. FENN, M.D.
CHICAGO HEIGHTS, ILL.

I

RELATION TO HEART RATE AND TO CLINICAL CONDITIONS ASSOCIATED WITH CHRONIC HYPERTENSION

Variations in the length of the different phases of the human electrocardiogram have long been observed, and satisfactory explanations have been offered for many of them by various writers. The length of the entire ventricular complex is known to vary in different individuals and in the same individual at different times but the explanation of this phenomenon has received comparatively scant attention at the hands of cardiologists.

The normal ventricular complex, the Q-R-S-T group, is usually divided into subgroups, the Q-R-S interval and the S-T interval. Prolongation of the Q-R-S interval is due to defects in certain portions of the conducting tissues. This fact has been established by animal experiment and by carefully controlled clinical observation. There are, however, certain cases in which the Q-R-S interval is normal but the Q-R-S-T interval exceeds the accepted time limit. It is with such cases that these studies have to deal.

Because of the great number of angles from which the subject must be approached, it was considered advisable to report separately on each investigation or group of investigations.

This report considers only those hearts in which the rhythm is regular and the rate approximately constant and under 120 per minute. The clinical conditions considered in this report may be termed chronic as they have existed in each individual over a long period of time. The measurements reported here were all made from Lead II of the electrocardiogram.

The results of the work in other fields of this investigation will follow.

Lewis [1] has defined the time relation of the Q-R-S group. He states that this group must have a duration of no more than 0.1 second, and that it usually constitutes less than one third of the entire ventricular complex. A critical review of the literature fails to reveal any carefully controlled work that places a definite time limit on the S-T

* From the Medical Service, St. Luke's Hospital, Chicago.

1. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1920.

interval without taking into consideration other features of the heart's activity. It is, therefore, safe to assume that the ventricular complex may normally vary in its length, and while the Q-R-S group is rather restricted in its variations, the S-T interval has much more latitude. This assumption is borne out in the study of electrocardiograms taken from normal individuals.

Garrod,[2] Thurston,[3] Chapman,[4] Eyster,[5] Einthoven [6] and others have pointed out the relation of the duration of the systole to the heart rate. Lombard and Cope [7] have devised a formula by which the systolic length may be predicted from the heart rate. Katz,[8] in carefully controlled animal experiments, has shown that the formula of Lombard and Cope may be used to predict the systolic length in animals whose heart rate is under 150.

In this work the prediction of the systolic length has been undertaken using a modification of the Lombard and Cope formula. The Q-R-S-T group is taken to represent ventricular systole. Wiggers and Clough [9] have shown that systole of the ventricle may be divided into two periods, the isometric period and the ejection period. The isometric period varies between 0.04 and 0.06 second, regardless of the heart rate or systolic length and is comparable to the Q-R-S group in that its limits of variation are narrow. Lewis [1] states that while the Q-R-S group begins before the actual contraction of the ventricle, the ventricular contraction has its inception sometime during the recording of the Q-R-S and ends within 0.03 second of the completion of the T. As the initial phase of ventricular activity is recorded 0.2 second or less before the contraction, the Q-R-S-T may be taken to represent the period of ventricular activity with a probable error of less than 0.05 second.

Lombard and Cope [7] devised the formula $S = \frac{60}{K\sqrt{R}}$ to determine the relation of systole to heart rate. In this formula S represents the systolic length in seconds, R the heart rate per minute and K a constant which they found varied with different positions of the body.

In studying the electrocardiogram it was found that the substitution of cycle length in seconds for heart rate per minute greatly facilitated matters. The heart rate is reciprocal of cycle length and may be expressed by the formula $R = \frac{60}{C}$, R being the heart rate per minute

2. Garrod, A. H.: J. Anat. & Physiol. **5**:17, 1871.
3. Thurston, Edgar: J. Anat. & Physiol. **10**:494, 1876.
4. Chapman, P. M.: Brit. M. J. **1**:511, 1894.
5. Eyster, J. A. E.: J. Exper. M. **14**:594, 1911.
6. Einthoven, W.: Arch. f. d. ges. Physiol. **122**:532, 1908.
7. Lombard, W. P., and Cope, O. M.: Am. J. Physiol. **49**:140, 1919.
8. Katz, L. N.: J. Lab. & Clin. M. **6**:291, 1921.
9. Wiggers, C. J., and Clough, H. D.: J. Lab. & Clin. M. **4**:624, 1919.

and C the cycle length in seconds. The original formula now becomes $S = \frac{60}{K\sqrt{\frac{60}{C}}}$. To simplify the equation both sides are squared resulting in $S^2 = \frac{60^2}{K^2 \frac{60}{C}}$ or $\frac{60C}{K^2}$. Extraction of the square root results in $S = \frac{\sqrt{60C}}{K}$. Up to this point the method followed was that suggested by Katz [9] in the plotting of his curves.

It now becomes necessary to determine the value of K for the electrocardiogram. This was done by measuring the systolic and cycle lengths of a number of electrocardiograms from normal individuals. The values of S and C being known, the equation becomes $KS = \sqrt{60C}$ and it appears that 20 is the proper valuation of K. The manner of arriving at this conclusion is shown in Table 1.

TABLE 1.—Manner of Determining Value of K in Formula $KS = \sqrt{60C}$

E. C. G. No.	Cycle Length C	Q-R-S-T Interval S	$KS = \sqrt{60\,C}$	K
9	0.59	0.30	$0.30\,K = \sqrt{3.54}$	19.7
12	0.78	0.33	$0.33\,K = \sqrt{46.8}$	20.8
17	0.68	0.32	$0.32\,K = \sqrt{40.8}$	20.0
41	0.88	0.35	$0.35\,K = \sqrt{52.8}$	20.7
47	0.70	0.32	$0.32\,K = \sqrt{42.0}$	20.3
56	0.80	0.34	$0.34\,K = \sqrt{48.0}$	20.2
81	0.80	0.36	$0.36\,K = \sqrt{48.0}$	19.2
138	0.84	0.36	$0.36\,K = \sqrt{50.4}$	19.8
143	0.68	0.32	$0.32\,K = \sqrt{40.8}$	20.0
106	0.68	0.33	$0.33\,K = \sqrt{40.8}$	19.5

These were cardiograms of known normal individuals.
Average value of K is 20.02.

Since $S = \frac{\sqrt{60C}}{K}$ and the value of K has been determined it is now possible to predict the normal duration of systole for any heart rate considered in this paper. The equation may now be further simplified and becomes $S = \frac{7.8\sqrt{C}}{20}$ or $S = .39\sqrt{C}$. The last formula is the one which is used in this study for the prediction of the Q-R-S-T interval.

Bazett,[10] in analyzing the relation of systole to cycle length, projected images of his electrocardiograms on a large sheet of millimeter

10. Bazett, H. C.: Heart 7:353, 1920.

ruled paper. In this way very accurate measurements were made possible. He evolved the formula $S = K\sqrt{C}$. He found that the value of K was 0.37 for men and 0.40 for women. After the publication of Bazett's results the cardiograms used in this series were reexamined and it was found that approximately one third were taken from women and two thirds from men.

Considering the fact that this work was done independently and by a different method from that of Bazett the results correspond exceedingly well.

It is apparent, then, that ventricular systole bears a definite relation to heart rate or cycle length, and it is evident that this fact must be considered before speculating on the significance of prolonged Q-R-S-T intervals. Evidence is here presented to show that unusually long Q-R-S-T intervals may be well within the calculated limits and the prolongation only a relative one. Table 2 shows a number of tracings in which the Q-R-S-T group measures 0.40 second or more and yet the calculated systole corresponds very closely with the measured one.

A further study of this series of tracings reveals that quite another condition may be present. The Q-R-S.T interval may have all the appearance of being normal in its duration but the application of the formula will show that it is prolonged beyond its predicted length. It may be within the accepted normal limits yet absolutely prolonged. Table 3 records a series of cardiograms in which the Q-R-S-T interval falls well within the usual normal limits. None of these intervals is prolonged beyond 0.40 second yet each of them is prolonged 0.05 second or more beyond the predicted length.

In selecting from the studied material those cardiograms in which the Q-R-S-T interval was definitely prolonged, none were chosen which did not show a prolongation of 0.05 second or more. The clinical conditions that seem to stand out preeminently as a cause for the increase in systolic length are those conditions associated with high blood pressure. Table 4 shows a number of tracings exhibiting this prolongation and in all of these cases the blood pressure is well above the normal.

Meakins [11] has published a series of cases in which the Q-R-S-T interval is prolonged and he calls attention to the frequent occurrence of high blood pressure. In Meakins' work, however, the relation of the systolic length to heart rate has not been sufficiently emphasized and it will be found that many of the apparently long systolic intervals correspond closely to the predicted lengths.

---

11. Meakins, J.: Arch. Int. Med. **24**:489 (Oct.) 1919.

TABLE 2.—LONG Q-R-S-T INTERVALS WHICH CORRESPOND CLOSELY TO THEIR PREDICTED LENGTHS

Patient	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
Mrs. N.	54	1.12	0.42	0.41	0.01+	Normal individual
G. G.	50	1.20	0.41	0.43	0.02—	Normal individual
G. Z.	50	1.20	0.44	0.43	0.01+	Diabetes mellitus
C. B.	30	2.00	0.55	0.55	0	Complete heart block
T. L.	49	1.23	0.44	0.43	0.01+	Chronic arthritis

TABLE 3.—Q-R-S-T INTERVALS WITHIN THE ACCEPTED NORMAL LIMIT WHICH ARE PROLONGED 0.05 SECOND OR MORE BEYOND THEIR PREDICTED LENGTH

E. C. G. No.	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
34	83	0.72	0.40	0.33	0.07+	Addison's disease
53	86	0.70	0.39	0.32	0.07+	Mitral disease
55	77	0.78	0.40	0.34	0.06+	Hypertension; arteriosclerosis
90	94	0.64	0.38	0.31	0.07+	Hypertension; cardiac hypertrophy
122	90	0.66	0.38	0.32	0.06+	Chronic cholecystitis
133	107	0.56	0.36	0.29	0.07+	Hypertension; uterine fibroids
154	100	0.60	0.37	0.30	0.07+	Diabetes mellitus
159	77	0.78	0.39	0.34	0.05+	Carcinoma of stomach
190	100	0.60	0.36	0.30	0.06+	Lung abscess
27W	83	0.72	0.39	0.33	0.06+	Pernicious anemia

TABLE 4.—Q-R-S-T INTERVALS FROM PATIENTS WITH HIGH BLOOD PRESSURE SHOWING PROLONGED SYSTOLE

E. C. G. No.	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
28	80	0.75	0.40	0.34	0.06+	Hypertension; mitral stenosis; S. 220, D. 104
40	107	0.56	0.34	0.29	0.05+	Hypertension; chronic nephritis; S. 210, D. 148
45	88	0.68	0.38	0.32	0.06+	Hypertension; mitral stenosis; S. 160, D. 102
55	77	0.78	0.40	0.34	0.06+	Hypertension; senile arteriosclerosis; S. 190, D. 110
90	94	0.64	0.38	0.31	0.07+	Hypertension; arteriosclerosis; S. 182, D. 102
133	108	0.56	0.36	0.29	0.07+	Hypertension; uterine fibroids; S. 200, D. 128
163	72	0.84	0.41	0.36	0.05+	Hypertension; chronic nephritis; S. 202, D. 130
191	73	0.82	0.40	0.35	0.05+	Hypertension; diabetes; S. 260, D. 150
196	83	0.72	0.40	0.33	0.07+	Hypertension; S. 180, D. 100
251	82	0.73	0.40	0.33	0.07+	Hypertension; S. 220, D. 10[illegible]

In this table S. represents systolic pressure and D. diastolic pressure.

Bowen [12] was the first to call attention to the augmented systolic length in the heart working against increased pressure. In his observations on normal individuals doing measured amounts of muscular work he found that as cycle length shortened with increased heart rate, the systolic length tended to become longer. As this observation was at variance with any previously reported, he carefully checked his apparatus to be sure that his results were real rather than apparent. After assuring himself of the correctness of his observations, he explained this phenomenon by comparing the heart to a simple pumping engine which slows when it meets an increased resistance. The rise in blood pressure which accompanies the beginning of muscular work furnished the increased resistance against which the heart must work.

More recently Patterson, Piper and Starling,[13] working with heart and lung preparations, have shown that heart volume, intracardiac pressure, and systolic length all increase to meet an increased arterial resistance. In their work it was possible to control all features so that the diastolic inflow could be kept at a constant level and by increasing the arterial resistance it was shown that the heart dilates and, in this process, the individual muscle fibers become lengthened. If the law of the heart muscle corresponds to that of skeletal muscle, that the energy set free on contraction depends on the initial length of the muscle fibers, then greater contractile stress and prolonged systole should result. This was found to occur in the work of Patterson, Piper and Starling.

These experiments serve very well to explan the prolonged Q-R-S-T interval in the patients in this study exhibiting high blood pressure. They also serve to show that ventricular systole measured by the electrocardiogram may be favorably compared to that measured by mechanical means.

It was observed, however, in this study, that many of the patients whose Q-R-S-T interval is not prolonged exhibit greatly increased blood pressures. Table 5 records a series of cases in which the blood pressure is high and yet the measured and predicted systolic lengths closely correspond.

A consideration of Tables 4 and 5 demonstrates clearly that factors other than a simple increase in the arterial resistance must operate to produce a prolongation of the Q-R-S-T interval.

In attempting to explain the lack of similarity in the behavior of different individuals, consideration must be given to the work of Wiggers [14] dealing with the relation of systolic length to heart rate, diastolic inflow and arterial resistance. He states that the duration of

12. Bowen, W. P.: Am. J. Physiol. **11**:59, 1904.
13. Patterson, S. W.; Piper, H., and Starling, E. H.: J. Physiol. **48**:465, 1914.
14. Wiggers, C. J.: Am. J. Physiol. **56**:439, 1921.

systole is prolonged by increased venous inflow, whether or not this increase is accompanied by a rise in arterial resistance. He found also that increase in the arterial resistance caused prolongation of systole only when the pressure causing the resistance was applied on the aorta near the semilunar valves. When the resistance was met with in the peripheral circulation or even in the abdominal aorta no lengthening of systole took place; indeed, the systolic length tended to become shorter. He concluded, further, that the duration of systole at a constant heart rate was dependent on the initial pressure in the ventricle rather than on the initial length of its fibers.

TABLE 5.—Q-R-S-T Intervals from Patients With High Blood Pressure Showing no Prolongation of Systole

E. C. G. No.	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
1	77	0.78	0.34	0.34	0	Mitral and aortic disease; S. 202, D. 120
17	88	0.68	0.32	0.32	0	Mitral and aortic disease; S. 182, D. 76
38	70	0.88	0.37	0.36	0.01+	Myocarditis; renal disease; S. 200, D. 140
80	84	0.72	0.34	0.33	0.01+	Hypertension; S. 202, D. 110
85	111	0.54	0.28	0.28	0	Acute alcoholism; hypertension; S. 162, D. 88
103	117	0.52	0.28	0.28	0	Abscess of nose; S. 180, D. 112
126	96	0.62	0.31	0.31	0	Aortic aneurysm; S. 160, D. 70
151	63	0.96	0.38	0.38	0	Hypertension; S. 250, D. 120
152	81	0.74	0.34	0.34	0	Hypertension; chronic nephritis; S. 238, D. 110
208	73	0.82	0.36	0.35	0.01+	Aortic disease; S. 182, D. 110

In this table S. represents systolic pressure and D. diastolic pressure.

In striving to apply these conclusions to the results obtained in the human electrocardiogram one must enter largely into the fields of speculation. It is obviously impossible to measure venous inflow and, while increased venous pressure may be estimated easily enough, an increase in the venous pressure does not necessarily carry with it an increased venous inflow into the ventricle. It would also be very difficult to determine the location of the etiologic factor in the production of an increased arterial resistance.

In spite of these difficulties it does not appear that increased initial tension in the ventricle will account for the prolongation of the Q-R-S-T interval in these patients. All of the patients, whose records appear in this report, had been carrying their vascular overload for a considerable period of time and they were subjected to no unusual stress at the time their cardiograms were made. Most of them, in fact, had been at rest for some time. Under these conditions it is improbable that there should be any increase in the initial tension in the ventricle for that particular heart.

Wiggers does not state whether the heart volume failed to increase when the pressure causing increased arterial resistance was applied at some distance from the aortic valves, but it is possible that heart volume would not increase if the pressure were applied for a comparatively short time.

In such an event the intervening arterial system would take care of the increased resistance so that there would be no increase in initial tension in the ventricle, as Wiggers states, and neither would there be increase in initial length of its fibers.

If, however, the factor, producing the increased resistance, continued to act over a long period of time, such as it must in the cases of chronic hypertension reported here, sooner or later the increased tension must make itself felt in the ventricle and with the increase in intraventricular pressure comes an augmented initial length of its fibers.

The conclusion is forced, therefore, that the duration of systole in hypertension is a measure of the initial length of the ventricular fibers and, to such an extent, a measure of its muscular dilatation.

It is possible to determine the effect on the Q-R-S-T interval of rapidly rising or falling blood pressures. Such a series of cases is under observation at the present time and will be reported on later.

It is probable that the variation in the behavior of different individuals is of prognostic value but these cases have not been under observation a sufficiently long time to venture a definite opinion on the prognostic significance of the Q-R-S-T interval. This will be reported on later.

SUMMARY AND CONCLUSIONS

1. It is possible to predict with a reasonable degree of accuracy the duration of systole in normal individuals.

2. Clinical conditions accompanied by high blood pressure are often associated with prolongation of the Q-R-S-T interval.

3. It is probable that this prolongation is of prognostic value, but from the data at hand at present a definite statement may not be made.

POSTOPERATIVE PULMONARY COMPLICATIONS *

ELLIOTT C. CUTLER, M.D., AND ALICE M. HUNT, R.N.
BOSTON

INTRODUCTION

It is with some hesitation that we again present this subject.[1] That there remains, however, considerable divergence in the minds of both surgeons and anesthetists as to the etiologic factors, and therefore, the prevention and treatment of pulmonary complications there is no doubt. The retiring president of the American Association of Anesthetists stated this Spring that only 3 per cent. of anesthetists considered such complications as embolic in origin and in the most recent textbook of medicine [2] aspiration is put forward as the chief cause of postoperative pneumonia. Previous studies had led us to believe that the majority of these lesions are infarcts and an analysis of the cases subjected to operation in this clinic during the past year brings additional evidence to support this view. The recent literature contains many excellent papers in agreement with this opinion, and we feel that it is unfortunate that anesthetists and anesthesia should bear the blame for such complications when the facts would seem to exonerate both, in the majority of cases.

The cases subjected to operation in this hospital during 1920 will form the basis for this report. Statistical reports are unquestionably open to criticism, the use of hospital records possibly more so than in other fields. For no matter how meticulously kept, when studied from the viewpoint of a researcher, much will be found missing. Moreover, let alone the fact that many of the observations are made by another worker, they are often inexact. This is an example of the practical impossibility of cooperative research. It may be said, however, that our previous interest in this subject [1] has made it possible to obviate some of the inaccuracies that can occur. In this clinic all patients are constantly watched for the appearance of such complications and the roentgen ray is generously used as a control. Moreover, when such a lesion does occur an additional diagnosis card is filed away for future reference so that all proven cases are easily available for study when desired.

As might be expected, this arrangement has enabled us to assemble a steadily increasing percentage of cases. Whereas in 1916 of 3,490 cases we [1] were able to identify only sixty-five with pulmonary compli-

---

* From the Surgical Clinic, Peter Bent Brigham Hospital.

1. *a.* Culter, E. C., and Morton, J. J.: Postoperative Pulmonary Complications, Surg., Gynec. & Obst. **25**:621, 1917. *b.* Cutler, E. C., and Hunt, A. M.: Postoperative Pulmonary Complications, Arch. Surg. **1**:114 (Jan.) 1920.

2. Lord, F. T.: Postoperative Pneumonia, Nelson's Loose Leaf System Med. **1**:296, 1920.

cations, during 1920 we found sixty-three cases among 1,604 cases, a difference in respective morbidity of from 1.86 to 3.92 per cent. This increasing morbidity is comparative to contemporary studies. McKesson [3] reported 3.03 per cent. morbidity among 39,438 collected cases in 1918. That the increasing morbidity figure is due to better records is further emphasized by the comparative drop in the mortality percentage.[4] In 1916 our cases showed a mortality percentage of morbidity of 50.7 as opposed to our present figures of 7.9. The cases studied in this report give an approximate morbidity of 1 in every 25 cases and an approximate mortality of 1 death in every 320 cases. Although this indicates a great decrease, these figures should still cause concern.

As in previous reports, patients with bulbar palsy or a terminal pneumonia, in association with definitely serious or fatal primary lesions, are excluded. Otherwise, all patients submitted to some form of operative procedure under anesthesia are included. The entire field of pulmonary complications is again studied since it appears that such studies are of greater value in that the etiology is often the same in the many varied clinical lesions and the clinical classification is difficult owing to a confusion in the signs and symptoms presented. Any attempted comparative study of statistical reports is open to the further criticism that in no two clinics are the conditions the same. That is particularly true of this very subject, and the report of a clinic such as this, in which the majority of patients are from the poorer classes of a large city, is not suitable for accurate comparison with a clinic such as that at Rochester, Minn.[5] Again, no comparison should be made with special clinics, as those given over to gynecology.[6] In a search, however, for the underlying pathology, all the material can be used since it is probable that no matter what the type of case or operation the mechanism resulting in pulmonary complications is the same.

The result of the present study appears to corroborate a previous report of ours[1] in which embolism from the operative field seemed to be the chief cause of pulmonary complications. In the present report each case was carefully scrutinized with a view to determining the

3. McKesson, E. I.: Some Observations on Postoperative Lung Complications, Am. J. Surg. **32**:16, 1918 (Quart. suppl. Anesth.).

4. The comparative studies at the Presbyterian Hospital with figures for 1898 (75), 1916 (81) and 1917 (82) show the same tendency to an increased morbidity and decreased mortality due to more accurate records. In 1898 Schultze reported 0.38 per cent. postoperative pneumonias, whereas in 1916 Whipple reported 2.6 per cent. of this complication.

5. *a.* Beckman, E. H.: Pulmonary and Circulatory Complications Following Surgical Operations, Mayo Clinic Papers, Philadelphia and London, W. B. Saunders Co., 1910, p. 594. *b.* Complications Following Surgical Operations, 1912, p. 738. *c.* 1913, p. 776.

6. Pfannenstiel, J.: Ueber die Vorzuge der Athernarkose, Zentralbl. f. Gynäk. **27**:8, 1903.

etiology of the lesion at the time of its occurence. Roentgen ray studies confirm the type and extent of the majority of these lesions.

REVIEW OF LITERATURE

Except for recent reports the literature pertaining to this field was fully covered in previous studies.[1] At that time reports covering the whole field of pulmonary complications were few although there were many excellent studies concerning the complications following laparotomy and the incidence of postoperative pneumonia alone. Table 1 includes the comparative figures for total pulmonary complications in the various clinics up to the present time.

TABLE 1.—TOTAL PULMONARY COMPLICATIONS

Clinic	Author and Year	No. of Cases	Pulmonary Morbidity		Pulmonary Mortality		Mortality per Cent. of Morbidity
			No.	Per Cent.	No.	Per Cent.	
Montreal General Hospital	Armstrong,[7] 1906	2,500	55	2.2	32	1.28	58.1
Von Eiselberg, Vienna	Ranzi,[8] 1908	6,871	263	3.8			
Combined statistics	Von Lichtenberg,[9] 1908	23,672	440	1.9			
Mayo Clinic *	Beckman,[6a] 1910	3,667	41	1.12	9	0.24	21.0
Mayo Clinic *	Beckman,[6b] 1912	5,835	92	1.57	6	0.10	6.5
Mayo Clinic *	Beckman,[6c] 1913	6,825	87	1.27	0	0.00	0.0
Massachusetts General Hospital	Cutler and Morton,[1a] 1917	3,490	65	1.86	33	0.94	50.7
Combined statistics	McKesson,[5] 1915	39,438	..	3.03	..	1.06	
Peter Bent Brigham Hospital	Cutler and Hunt,[1b] 1920	1,562	55	3.52	11	0.7	20.0
Pittsburgh	Decker,[10] 1921	5,976	69	1.2	29	0.5	42.0
Peter Bent Brigham Hospital	Cutler and Hunt, 1921	1,604	63	3.92	5	0.31	7.93

* Amended to include pulmonary embolism.

The chronologic order of the data in this table demonstrates graphically the increasing morbidity with its concomitant decrease in mortality. The figures of Decker alone disagree. The reason for this appears to be a failure to include minor complications. It is indeed almost impossible to arrive at accurate data unless each case is studied from this viewpoint and checked, at the time of occurrence, for future reference.

The discussion of the etiology of these complications has brought to light two opposing views,—one, that the anesthetic and the other that embolism plays the chief rôle. That inhalation anesthesia produces some irritation, and that the aspiration of mouth contents occurs there

7. Armstrong, G. E.: Remarks on Lung Complications After Operations with Anesthesia, Brit. M. J. **1**:1141, 1906.

8. Ranzi, E.: Ueber postoperative Lungenkomplikationen embolisher Natur, Arch. f. klin. Chir. **87**:380, 1908.

9. Lichtenberg, A.: Die postoperativen Lungenkomplikationen, Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **11**:129, 1908.

10. Decker, H. R.: Postoperative Complications and Sequels of the Respiratory Tract, Penn. M. J. **24**:391, 1921.

can be no doubt (Hoelscher [11] and Kelly [12]). That a perfectly smooth inhalation anesthesia reduces such undesirable sequels is vigorously upheld (Poppert,[13] Offergeld,[14] von Lichtenberg,[15] Ladd and Osgood,[16] Magaw,[17] Bevan,[18] Kroenlein,[19] Keen,[20] Herb,[21] Henderson [22]). This, however, fails to explain why, with local anesthesia, the proportion of such complications is equally high (Gottstein,[23] Mikulicz,[24] Henle [25] and Sauerbruch [26]). It also fails to explain why with anesthesia in expert hands these complications continue to occur.[27]

The statement [2] that aspiration is the chief cause of postoperative pneumonia is not proven by the facts. There is an increasing mass of evidence demonstrating the frequency of postoperative embolism and its relation to pulmonary complications. W. J. Mayo [28] states that

---

11. Hoelscher, R.: Experimentelle Untersuchungen über die Entstehung der Erkrankungen der Luftwege nach Aethernarkose, Arch. f. klin. Chir. **57**:175, 1898.

12. Kelly, R. E.: Anesthesia by the Intratracheal Insufflation of Ether, Brit. M. J. **2**:112, 617, 1912.

13. Poppert: Experimentelle und klinische Beiträge zur Aethernarkose und zur Aetherchloroform Mischnarkose, Deutsch. Ztschr. f. Chir. **67**:505, 1902.

14. Offergeld: Lungenkomplikationen nach Aethernarkosen, Arch. f. klin. Chir. **83**:505, 1907.

15. Lichtenberg, A.: Experimenteller Beitrag zur Frage der Entstehung der Pneumonie nach Narkosen, München. med. Wchnschr. **53**:2286, 1906.

16. Ladd, W. E., and Osgood, G.: Gauze-Ether, or a Modified Drop Method, with Its Effects on Acetonuria, Ann. Surg. **46**:460, 1907.

17. Magaw, A.: A Review of Over Fourteen Thousand Surgical Anesthesias, Surg., Gynec. & Obst. **3**:795, 1906.

18. Bevan, A. D.: The Choice and Technic of the Anesthetic, Tr. Am. Surg Assn. **33**:21, 1915; **29**:177, 1911.

19. Kroenlein, R. V.: Discussion, Verhandl. d. deutsch. Gesellsch. f. Chir. **34**:131, 1905.

20. Keen, W. W.: The Dangers of Ether as an Anesthetic, Boston M. & S. J. **173**:831, 1915.

21. Herb, I.: Ether: Simplicity in Its Administration, J. A. M. A. **66**:1376 (April 29) 1916.

22. Henderson, F.: Ether Anesthesia, Collected Papers Mayo Clinic, Philadelphia and London, W. B. Saunders Co., 1913, p. 701.

23. Gottstein, G.: Erfahrungen über lokale Anästhesie in der Breslauer Chirurgischen Klinik, Arch. f. klin. Chir. **57**:409, 1898.

24. Mikulicz, J.: Die Methoden der Schmerzbetäubung und ihre gegenseitige Abgrenzung, Verhandl. d. deutsch. Gesellsch. f. Chir. **30**:560, 1901.

25. Henle: Die Methoden der Schmerzbetäubung und ihre gegenseitige Abgrenzung, Verhandl. d. deutsch. Gesellsch. f. Chir. **30**:240, 1901.

26. Sauerbruch, F.: Der Stand der Klinischen und Operativen Chirurgie, Beitr. z. klin. Chir. **122**:234, 1921.

27. This statement will be objected to by many. Only let these consider that in most large institutions and especially in those from which reports come, anesthesia is in really expert hands now. Yet these complications continue. Also let them take into consideration that a betterment of operative technic has also taken place and consider that a reduction in such complications may be due to this factor quite as well as to the improvements in the administration of anesthesia.

28. Mayo, W. J.: Mortality and End Results in Surgery, Surg., Gynec. & Obst. **32**:97, 1921.

minute septic emboli from the operative field are a common cause of secondary pulmonary complications. He laments that these complications are too frequently attributed to the anesthetic, and says that they are quite as frequently found in cases in which local anesthesia is employed. The recent illuminating papers of Ochsner and Schneider,[29] Hampton and Wharton,[30] Capelle,[31] McCann[32] and Rupp[33] demonstrate both the mechanism of thrombosis and embolism subsequent to operation and the great frequency of this condition as a source of pulmonary complications. These ideas are by no means of recent origin, and a study of the papers by Zahn,[34], Miller,[35] Gebele,[36] Otte,[37] Zurhelle,[38] Homans,[39] Michaelis,[40] Henderson,[41] Grant[42] and Eisenreich[43] reveals statistics and studies in support of this view. Zahn's paper, written in 1897, discusses the part passive congestion in the lung during operation may have as increasing the liability to infarction. In addition to such direct contributions are the many excellent reports both clinical[44] and experimental on fatal pulmonary embolism and pulmonary infarction. The experimental and pathologic studies of pul-

29. Ochsner, A. J., and Schneider, C. C.: Fatal Postoperative Pulmonary Thrombosis, Ann. Surg. **72**:91, 1920.

30. Hampton, H., and Wharton, L. R.: Venous Thrombosis, Pulmonary Infarction and Embolism Following Gynecological Operations, Bull. Johns Hopkins Hosp. **31**:95, 1920.

31. Capelle: Einiges zur Frage der Postoperativen Thromboembolie, Beitr. z. klin. Chir. **119**:485, 1920.

32. McCann, F.: Suggestions for the Prevention of Postoperative Thrombosis and Embolism, Brit. M. J. **1**:277, 1918.

33. Rupp, A.: Postoperative Thrombose und Lungenembolie, Arch. f. klin. Chir. **115**:672 (March) 1921.

34. Zahn, F. W.: Ueber die Folgen des Verschlüssens der Lungenarterien und Pfortaderaste durch Embolie, Verhandl. d. Gesellsch. deutsch. Naturforsch. u. Aerzte **19**:9, 1897.

35. Miller, R. B.: The Significance of Postoperative Pleurisy: Its Relation to Pulmonary Embolism, Am. Med. **4**:173, 1902.

36. Gebele: Ueber Embolische Lungen Affektionen nach Bauchoperationen; Eine klinisch-experimentelle Studie, Beitr. z. klin. Chir. **43**:251, 1904.

37. Otte, A.: Ueber die postoperativen Lungenkomplikationen und Thrombosen nach Aethernarkosen, München. med. Wchnschr. **54**:2473, 1907.

38. Zurhelle, E.: Thrombose und Embolie nach Gynäkologischen Operationen, Arch. f. Gynäk. **84**:443, 1908.

39. Homans, J.: Postoperative Pulmonary Complications, Bull. Johns Hopkins Hosp. **20**:128, 1909.

40. Michaelis: Zur Frage des Praemonitorischen Symptoms von Thrombose und Embolie, Ztschr. f. Geburtsh. u. Gynäk. **70**:285, 1912.

41. Henderson, F.: St. Paul M. J. **16**:74, 1914.

42. Grant, H. H.: Thrombophlebitis and Pulmonary Embolism, Mississippi Valley M. J. **30**:217, 1918.

43. Eisenreich, O.: Embolism After Gynecologic Operations, Monatschr. f. Geburtsh. u. Gynäk. **53**:190, 1920.

44. Wilson, L. B.: Fatal Postoperative Embolism, Collected Papers Mayo Clinic, Philadelphia, W. B. Saunders & Co., 1912, p. 727.

monary infarction are well covered by Welch,[45] McCallum,[46] Karsner and Ash [47] and Karsner and Austin.[48] That these postoperative lesions are usually situated in the lower lobes, more frequently on the right side than on the left, and thus comparable to pathologic studies on embolism and infarction may be carried as an additional argument for this mechanism. Indeed, to one familiar with the literature it is difficult to accept aspiration as the chief factor in such complications unless infarction can be disproved. The papers referred to present excellent discussions of the clinical signs and suggest prophylactic measures. With these ideas both our studies of 1919 and 1920 seem to agree and bring additional proof.

Etiologic factors other than the two cited may be considered of secondary importance. A focus of pulmonary disease existing at the time of operation unquestionably is the cause, at times, of a subsequent complication. The flare-up of a quiescent tubercular lesion or of an old bronchitis under inhalation anesthesia is unquestioned. Such lesions, however, do not always light up, and the fact that equally following operations under local anesthesia activity may be stirred up suggests the possibility of embolism as the direct cause even in such cases. The fact that the embolus reaches an already injured field makes its influence the more marked.

The importance of sepsis as a secondary factor cannot be denied, and there are cases with septic abdominal lesions in which, following operation, the lung is involved by direct extension. That a lymphatic avenue is open for such extension has been shown by the anatomic studies of Sabin,[49] Cunningham [50] and Miller.[51] The importance of sepsis both in the initiation of and the setting free of thrombi is an old story. The danger which it adds to embolism is manifest. Many cases of lung abscess following tonsillectomy usually have been thought to be due to the inhalation of mouth infectious material owing to position.

---

45. Welch, W. H.: An Area of Coagulative Necrosis Resulting from Shutting Off of the Blood Supply in an Infarct, Papers and Addresses, Baltimore, The Johns Hopkins Press **1**:110, 1920.

46. McCallum, W. P.: Infarction, A Textbook of Pathology, Ed. 2, Philadelphia and London, W. B. Saunders & Co., 1920, p. 33.

47. Karsner and Ash: Studies in Infarction, Experimental Bland Infarction of the Lung, J. M. Research **22**:1912-1913.

48. Karsner and Austin: Studies in Infarction, J. A. M. A. **57**:951 (Oct. 10) 1911.

49. Sabin, F. R.: The Method of Growth of the Lymphatic System, Science, New York **44**:145, 1916.

50. Cunningham, R. S.: On the Development of the Lymphatics in the Lungs of the Pig, Proc. Am. Assn. Anat., Anat. Rec. **9**:69, 1915.

51. Miller, W. S.: Some Essential Points in the Anatomy of the Lung, Am. J. Roentgenol. **4**:269, 1917. The Vascular Supply of the Pleura Pulmonalis, Am. J. Anat. **7**:389, 1908.

The recent report of W. B. Porter [52] concerning such lesions following local anesthesia, and his suggestion of the logical embolic route is of interest in this relation. And Burnham's [53] paper on pleurisy and empyema evidences the importance of a septic focus. In all his cases in which empyema developed the original operation was for a septic abdominal lesion.

Acidosis has been considered as having an influence in the production of these lesions. There has been, however, no satisfactory explanation of the mechanism by which this produces its effect, and some investigators [54] have denied its existence. It is possible that where asphyxia is produced there is some acidosis, and thereby the natural resistance to infection is lowered. Whether this is due to the anesthetic [55] or to the effects of the operation [56] is unknown.

Chilling and cold possibly produce some effect in a similarly remote manner. The work of Miller and Noble,[57] Hill [58] and Mudd and Grant [59] would appear to show that there is some lowered resistance to infection with chilling. Moreover, such clinical investigators as Boothby,[60] Homans,[39] Keen,[20] Armstrong,[7] Gerulanos,[61] and Decker [10] have felt that either external exposure or chilling by cold wet packs during operation played a part in the subsequent pulmonary complications.

These factors, by the production of a lowered immunity, may open the body to attack by organisms commonly present. That Group IV pneumococcus is commonly found in these cases (Whipple [62] and Cleve-

52. Porter, W. B.: Pulmonary Abscess Following Tonsillectomy Under Local Anesthesia, Virginia M. Month. **47**:606 (March) 1921.

53. Burnham, A. C.: Postoperative Pleurisy with Effusion and Empyema, Surg., Gynec. & Obst. **19**:468, 1914.

54. Caldwell, G. A., and Cleveland, M.: Observations on the Relation of Acidosis to Anesthesia, Surg., Gynec. & Obst. **25**:22, 1917.

55. Carter, W. S.: Effect of Ether on the Alkali Reserve, Arch. Int. Med. **26**:319 (Sept.) 1920. Collip, J. B.: Effect of Surgical Anesthesia on the Reaction of the Blood, Brit. J. Exper. Path. **1**:282, 1920. Jeanbrau, E., Cristol, P., and Bonnet, V.: Anesthesia and Acidosis, J. d'urol. méd. et. chir. **11**:505 (May-June) 1921.

56. Farrar, L. K. P.: Acidosis in Operative Surgery; Occurrence During Operation and Its Treatment by Glucose and Gum Acacia Given Intravenously, Surg., Gynec. & Obst. **32**:328, 1921.

57. Miller, J. A., and Noble, W. C.: The Effects of Exposure to Cold on Experimental Infection of the Respiratory Tract, J. Exper. M. **24**:223, 1916.

58. Hill: The Influence of the Atmospheric Environment on the Respiratory Membrane, Brit. M. Research Committee, Ser. 32, p. 141, 1919.

59. Mudd, S., and Grant, S. B.: Reactions to Chilling of the Body Surface, J. M. Research **40**:53, 1919.

60. Boothby, W. M.: Postoperative Pneumonia (Discussion) J. A. M. A. **67**:539 (Aug. 12) 1916.

61. Gerulanos, M.: Lungen Komplikationen nach Operativen Eingriffen, Deutsch. Ztschr. f. Chir. **57**:371, 1898.

62. Whipple, A. O.: A Study of postoperative Pneumonia in the Presbyterian Hospital During 1915, Med. Rec. **89**:581, 1916. A Study of Postoperative Pneumonitis, Surg., Gynec. & Obst. **26**:29, 1918.

land [63]), might seem to be additional evidence that this mechanism existed. It should, however, be recognized that Group IV pneumococcus is commonly found in normal mouths (Stillman,[64] Dochez and Cole [65]). Provided, that a focus of pulmonary disease already existed, this lowered resistance might enable organisms present to get a start and thus a more virulent mixed type of infection might occur.[66]

It is difficult, however, to appreciate the importance of such secondary factors, and also that aspiration is the chief factor, when it is so well known that the experimental production of pneumonia by the bronchial route is extremely difficult. Blake and Cecil's [67] studies alone seem to be successful by this method, except when enormous dosage has been used.

The foregoing facts may be taken as a defense of inhalation anesthesia and anesthetists. It is astonishing that so few of the latter have attempted their own defense when the general concensus of opinion now definitely favors embolism as the chief factor in the production of these lesions. The earlier reports on "ether pneumonia" cast a most unjust opprobrium on the anesthetic. That venous thrombosis, fatal pulmonary embolism and pulmonary infarction are common there can be no doubt. McCallum [46] and Welch [45] have given admirable descriptions of the underlying pathology. The right lower lobe is most frequently the site of both these clinical lesions and the pathologic types recorded. Moreover, infarction can be the only explanation in cases in which local anesthesia is used. Why search for additional factors when the pathologic and clinical studies emphasize the importance and frequency of embolism, and when the clinical picture is far more frequently of the type ascribable to this factor?

As is shown in the cited reports, and as the cases presented later show, the onset in the majority of these cases is abrupt, dissimilar to the onset of infection elsewhere, and the subsidence, except when the embolus has arisen in a septic field or landed in a focus of pre-existing pulmonary disease, is almost equally rapid. Moreover, the symptom of pain, the small areas involved and the typical lobular distribution of

63. Cleveland, M.: Further Study in Postoperative Pneumonitis, Surg., Gynec. & Obst. **28**:282, 1919.

64. Stillman, E. G.: A Contribution to the Epidemiology of Lobar Pneumonia, J. Exper. M. **24**:651, 1916.

65. Dochez, A. R., and Cole, R. I.: Pneumococcus Infection, Forchheimer's Therapeusis of Internal Diseases, New York and London, D. Appleton & Co., **5**:472, 1914.

66. Wadsworth, A. B.: Experimental Studies on the Etiology of Acute Pneumonitis, Am. J. M. Sc. **127**:851, 1904. A Study of Experimental Organizing Pneumonia, J. M. Research **34**:147, 1918.

67. Blake, F. G., and Cecil, R. L.: Production of Pneumococcus Pneumonia in Monkeys, J. Exper. M. **31**:403, 1920. Pathology and Pathogenesis of Pneumococcus Lobar Pneumonia in Monkeys, J. Exper. M. **31**:445, 1920.

the lesion, with often cone-shaped roentgen-ray shadows, is so striking as to leave little doubt as to the kind of lesion present.

PRESENTATION OF MATERIAL

From Jan. 1, 1920, to Jan. 1, 1921, 1,604 cases [68] in this clinic were submitted to some form of operative procedure under anesthesia. Sixty-three of these patients developed a pulmonary complication that might be attributable to the operative intervention or to the anesthetic. There were five deaths among these sixty-three cases. In addition five other patients died with pulmonary lesions following operation, but three of these suffered from bulbar paralysis due to intracranial lesions and two were old men, admitted "in extremis," with septic genito-urinary lesions, who, after some simple emergency intervention developed septicemia with its concomitant terminal pneumonia. It appears only fair to remove such cases from this discussion. Thus in 3.93 per cent. of the cases (one in twenty-six) a complication developed and 0.3 per cent. (1 in 321) patients died from one of the complications.

The conception that small emboli from the operative field are the chief etiologic factors makes the classification simpler. All cases in which this mode of occurrence was obvious can be placed in a distinct class. We have elected to term these, cases of pulmonary infarction. The further divisions are, lobar and bronchopneumonia, bronchitis, pleurisy, pulmonary embolism, empyema, lung abscess and cases in which there has been exacerbation of a tuberculous lesion.

We found that unless a separate division was made for the embolic cases the greatest difficulty in classification arose. Thus many lesions, in which this mechanism was obvious, simulated partly pleurisy, there being pain and a friction rub, and partly pneumonia, since a small patch of consolidation was demonstrable both on physical examination and by the roentgen ray. In this report, therefore, we have placed in the class termed infarction all those cases in which the mechanism of embolism was undoubted (excepting the typical fatal pulmonary embolism cases). Ranzi [8] called these small embolic lesions embolic pneumonia, a somewhat confusing pathologic term. In the other classes we feel there must be also some cases in which embolism was present, but either the presence of sepsis in the wound or a preexisting pulmonary lesion so confused the picture that classification as infarction was not justifiable.

Pathologists regard as pulmonary infarction only those lesions that go on to coagulative necrosis. Thus they may object to this nomenclature. The mechanism of these minor infarctions, however, is the

68. This does not include cystoscopies, dressings and the applications of plaster cast unless anesthesia was employed.

same as with larger coagulative necrotic lesions and certainly both in etiology and pathology the lesions are more nearly infarction than true pneumonia. Observers in the past, including ourselves, by classifying such lesions as pneumonia have certainly not clarified the issue. It is our hope that the submitted evidence in regards to such lesions will lead others to adopt the same classification. If this is followed it would appear that a better understanding of pulmonary complications as a whole must result.

TABLE 2.—Morbidity and Mortality of Various Complications

Complications	No. of Cases	Morbidity Percentage	No. of Deaths	Mortality Percentage of Morbidity	Approximate Morbidity per 100 Cases	Approximate Mortality per 100 Cases
Lobar pneumonia	1	0.06	1	100	1:1604	1:1604
Bronchopneumonia	7	0.43	1	14.2	1:229	1:1604
Bronchitis	16	0.99	0	0	1:100	0
Exacerbation of tuberculosis	2	0.12	0	0	1:804	0
Pleurisy	2	0.12	0	0	1:804	0
Empyema	1	0.06	1	100	1:1604	1:1604
Pulmonary infarction	32	1.99	0	0	1:50	0
Pulmonary embolism	2	0.12	2	100	1:804	1:804
Totals	63	3.92	5	7.93	1:25	1:320

Table 2 depicts the great preponderance of infarction cases. The freedom of this group from fatalities will be discussed later. It is clear, however, that in these cases death is due either to a large pulmonary embolism (a separate class) or to septic lesions. Here the confusion in the picture may place the case in the pneumonia or bronchitis class.

The infrequency of true lobar pneumonia is striking and further emphasizes the general tendency in the more accurate recent studies wherein lobar pneumonia is shown gradually to be disappearing as a postoperative lesion. This is especially true when the clinical findings have been verified by roentgen-ray studies. The reason for this lies in the mechanism of its production, i. e., embolism rather than infection.

Lobar Pneumonia.—There was only one case this year in which the complication was of the lobar pneumonia type. It is only fair to state that without the roentgen-ray studies we should have misplaced even this one case among the bronchopneumonias.

History.—Patient, 50 years of age, was operated on for an indirect left inguinal hernia under procain. Local anesthesia was used since the past history and physical examination indicated an already damaged lung. Three years previously the patient had suffered from a severe attack of pneumonia and ever since had been much troubled with asthma and frequent attacks of pleurisy. Moreover, physical examination of the lungs demonstrated relative dulness in the right upper lobe and many sonorous and musical râles throughout the entire right chest. Within two days following operation there was evident difficulty in breathing and some productive coughing. This increased and the

temperature and respiratory rate began to climb. By the fourth day postoperative there was a demonstrable area of consolidation in the right lower chest. Roentgen-ray studies on the eleventh day showed that all three lobes were uniformly involved, another roentgen-ray examination made on the eighteenth day showed beginning resolution in the upper and lower lobes but no change in the middle lobe. Shortly following this the urinary output diminished and the patient's general condition rapidly deteriorated. He died on the thirtieth day after operation.

This case is presented in some detail because it is both typical and atypical; typical in that a pre-existing focus of pulmonary disease flared up into a serious and fatal complication; atypical in that the lesion was lobar rather than lobular. Indeed, were it not for the excellent roentgen-ray studies, we had sufficient other clinical evidence to designate it a bronchopneumonia. The explanation of the fatality must lie in some connection with the previous attack of pneumonia, the patient's individual susceptibility and the possibility that he still harbored a malignant organism. One may suppose, however, that in the absence of inhalation irritants, emboli from the field of operation may have been the means of stirring into activity an already prepared focus of disease.

Bronchopneumonia.—We have placed seven cases in this group. All cases showed multiple areas of consolidation at some period following operation. There was one fatality. The anesthesia was gas-oxygen in four cases and ether in three. In two of the gas-oxygen cases, a little ether was given for added relaxation while opening the abdomen. In the straight ether cases, the open mask method was used twice and the Connell machine with an intranasal pharyngeal tube once. The operations were: laparotomy, six times, three times for appendicitis and once each for gastric ulcer, salpingitis and hydronephrosis, and craniotomy for extracerebellar acoustic neuroma once. The latter case ended fatally. The well known relative predominance of such complications with abdominal operations is thus exemplified.

The cranial case was of unusual interest to us in that we have rarely observed pulmonary complications in such cases, except when there has been ninth nerve involvement, which apparently was not present in this case. However, following a long, tedious, suboccipital operation this nerve may, to some extent, have been injured. The patient was 47, a good risk and did well following operation until the seventh day when without previous intimation there was a sudden rise in pulse, temperature and respiration. Bilateral basal bronchopneumonia progressed steadily until death on the twenty-fourth day postoperative. The sudden onset, although without pain, suggests the possibility of embolic origin of the complication. The large vessels encountered in such explorations are an obvious source of such thrombi.

The other six cases have both sepsis and abdominal section in common, a well recognized dangerous combination.[69] The three appendix cases were all acute either with abscess or perforation, the case of salpingitis was equally acute, a large pyosalpinx having ruptured and given the signs of a general peritonitis, and the gastric ulcer case with a sleeve resection for a pyloric lesion certainly holds infectious possibilities. The lungs were clear before operation in all but one case. The complications were confined to the bases in all cases, bilateral in one case, left side twice and at the right base three times. The time of onset varied from immediately following operation to the end of the first week. It should be said, however, that in all septic cases the recognition of a concomitant complication is always delayed and difficult because of the already existent picture of disease. In two cases only was the onset of the complication striking from a study of the chart. One of these began on the second and one on the eighth day after operation. The majority of these patients had a productive cough due, apparently, to a mild associated bronchitis. The presence of sepsis makes it difficult to explain the underlying etiology. It does not seem reasonable, however, to suppose that aspiration has produced this untoward effect only in such septic cases and the lobular rather than lobar distribution of the lesions gives us encouragement to believe that minute septic emboli may be at the bottom of the trouble in these cases. Or the infection may have progressed by direct extension.

Bronchitis.—In this group are sixteen cases, and, as a whole, they form a very distinctive picture. The whole field of surgery is covered, both septic and aseptic; six patients were operated on for hernia; the other operations, except for one each on the breast and thigh, were for varying abdominal conditions. Septic lesions were present in more than half the cases, and the patients were of all ages and both sexes. Ether was given in eleven cases and gas-oxygen in five.

In eleven cases there was evidence of previously existent pulmonary disease either in the past history or in the physical examination. This usually was a chronic, intermittent, troublesome bronchitis. And this appears to be of the greatest importance. There are undoubtedly many cases among all pulmonary complications, like those in this group, in which the development of complications can justly be charged to the

69. See the excellent papers of Bibergeil,[70] Läwen[71] and Robb and Dittrick[72] in which the high percentage of such complications following laparotomy is demonstrated and discussed.

70. Bibergeil, E.: Ueber Lungen Komplicationen nach Bauch Operationen, Arch. f. klin. Chir. **78**:339, 1905.

71. Läwen, A.: Ueber Lungenkomplikationen nach Bauchoperationen, Beitr. z. klin. Chir. **50**:501, 1906.

72. Robb and Dittrick: Pulmonary Complications Following Abdominal Operations, Surg., Gynec. & Obst. **3**:51, 1906.

anesthetic. In such cases the irritation of a pulmonary anesthesia is sufficient to flare up a quiescent lesion. However, it must be understood thoroughly that the existence of such a focus does not always entail postoperative disease. By making roentgenograms in a large series of cases before and after operation, irrespective of signs and symptoms, we have been able to prove to ourselves that many times such foci are present before operation and yet undergo no demonstrable change after inhalation anesthesia. Just what the criteria are that determine whether a case shall become active is not clear, but the fact that in three of these sixteen cases the sudden and late onset of the disease pictured the symptomatology of small emboli may mean that in a certain proportion of these lesions, clinically recognized as bronchitis, the flare-up is due to minute emboli from the operative field that land in an already prepared area. In one of the cases classified here as bronchitis an uneventful convalescence occurred until the eighth day when a careful physical examination, done to explain a rise in temperature, revealed a few râles at the base of the right lung. Such a case might possibly have been better classified under pulmonary infarction.

The majority of cases in this group are typical of postoperative bronchitis, showing an immediate respiratory distress with a good deal of cyanosis, frothy sputum and widespread râles. The upright position and warm vapor inhalation proves of much benefit. In cases in which any cardiac damage is suspected digitalis may be of assistance.

Exacerbation of Tuberculosis.—There are two cases in this year's complications in which, subsequent to operation, an acute pulmonary tuberculosis developed. One patient had acute appendicitis, the other had tuberculous lymphadenitis. In the appendix case ether was given as the examination had revealed no pulmonary disease; in the second case, both the physical signs and a chest roentgenogram gave warning and gas-oxygen was used. Both patients developed almost immediately following operation the signs of bronchopneumonia which were corroborated by roentgen-ray studies which also confirmed the presence of chronic lesions in the apices. Such a flare-up must be expected in a certain percentage of patients with this condition. These cases are presented here to emphasize the importance of pre-existent nontuberculous pulmonary disease as exemplified in the bronchitis group of cases just discussed. Thus, a warning is sounded concerning casual pre-operative pulmonary examination. In all such cases the anesthetic of choice is local; next choice, gas-oxygen.

Pleurisy.—Because of our adoption of infarction as a class of pulmonary complication we find that the simple pleurisy class is very small. However, it seemed wisest that the embolic lesions resulting in symp-

toms that chiefly resemble pleurisy should be grouped with those larger lesions that sometimes resemble pneumonia. We have, therefore, only classified two cases this year as pleurisy. These are both of the serous type and due to direct extension of infection from intra-abdominal disease.[50] One case occurred in a case of splenic abscess and one in a case of high retrocecal appendix. At a late period during convalescence respiratory pain led to a chest examination with the subsequent finding of a straw colored fluid in both cases. In one organisms (streptococcus) were present and the chest was repeatedly aspirated. Both patients made good recoveries and were discharged well.

The etiology of such cases is manifestly direct extension through the diaphragm. The work of Sabin [49] and Miller [51] demonstrates the avenues along which such extension may occur.

Empyema.—One case of postoperative empyema occurred. The case was one of cholelithiasis (common-duct stone) in a man, aged 72. Apparently because of insufficient local resistance an abscess developed in the field of operation, gravitated down to the kidney and then spread upward until a large subphrenic abscess formed. This finally ruptured into the pleural cavity. The mechanism of the etiology in this case is exactly that causing serous pleurisy, only more obvious and direct. It needs no explanation.

Pulmonary Infarction.—We have placed thirty-two of the total sixty-three complications in this group. The great relative size of this group needs explanation for it is somewhat of a diversion from the accepted classification of postoperative pulmonary disease. To all, however, who are familiar with the difficulties of such classifications, this group will be well understood.

In the past there have been many excellent papers on the embolic origin of these complications. In most of such these lesions of embolic origin, unless fatal, have been termed pneumonia. There have remained, however, certain minor lesions, quite evidently of the same origin, which have been designated pleurisy, and further, certain of the other classes of complication, as empyema and lung abscess, have been known to be embolic in origin. We have long felt that the present method of classification was unsatisfactory. Evidently, such lesions are not a true pneumonia, and, furthermore, there were many borderline cases which we found the greatest difficulty in classifying as either pneumonia or pleurisy. Morever, as will be shown later, these cases form a group with a rather typical clinical picture. The onset is usually abrupt, the physical signs are characteristic, and the subsidence is sudden, except when the emboli have arisen in a septic field. As discussed above under pneumonia, sepsis in the wound obscures the onset, the typical picture and the subsidence of such lesions. When septic emboli

are present, the clinical picture may simulate pneumonia or lung abscess may result, but when the clot is sterile, the resultant changes are characteristic of minor pulmonary infarction.

There are no fatalities in these thirty-two cases. All ages and both sexes are included. All but seven cases were laparotomies. The other operations were one each for varicose veins, cancer of the tongue, cancer of the breast, urethral stricture, tonsillectomy and two cranial explorations. Anesthetic: procain, once; gas-oxygen, seven times; ether, twenty-four times.

The clinical picture of all cases bears a close relationship. The onset may occur from the second day to the third week, usually with sudden pain on respiration, followed by expectoration in about one-half the cases. The sputum is often blood tinged. Preceding the onset of symptoms there is usually a rise in pulse, temperature and respirations, and with the pain these may increase. Immediate auscultation of the chest reveals one or more small areas filled with fine râles over which there is some impairment of breath sounds and, if the focus is sufficiently large, some change in fremitus. When pain is present a friction rub may be the most distinct sign. However, it must be remembered that although this is a characteristic sign when present it is so only because it creates pain and thereby directs attention to that part. A friction rub results only when the area of the infarct reaches the periphery of a lobe, and it must be understood if we are to recognize all these lesions, that some of the smaller thrombi do not cause sufficiently large infarcts to do this.

We have long felt that infarction can occur early or even immediately on recovery from operation. Cases have been observed in which characteristic signs were present on recovery from ether with chest pain, friction rub, bloody sputum and a demonstrable area of consolidation both by physical signs and the roentgen ray. In this year's series the onset in twenty-one of the thirty-two cases was within the first four days and in six cases it was within twenty-four hours.

Roentgen-ray studies should always be made and are often of the greatest value. Invariably they will demonstrate small areas of consolidation which from time to time will take the form of a cone-shaped shadow with its base out. Roentgen-ray studies, morever, should be made immediately, since these lesions chiefly represent merely a change in blood distribution and soon clear up. The adjustment to normal is complete, as a rule, within six or seven days.

In order to demonstrate more completely our conception of these lesions, the following cases with their charts and roentgen-ray studies are presented.

REPORT OF CASES

CASE 1 (P. B. B. H. Surg. No. 13020).—J. B., aged 25, single.

Diagnosis.—Right indirect inguinal hernia.

Operation.—Aug. 25, 1920, procain, 1 per cent.; Dr. Cutler. On the first day after operation the patient complained of severe pain in his back; his temperature kept rising and there was evident respiratory difficulty. Morphin and digitalis were administered to control pain and coughing. Examination of the

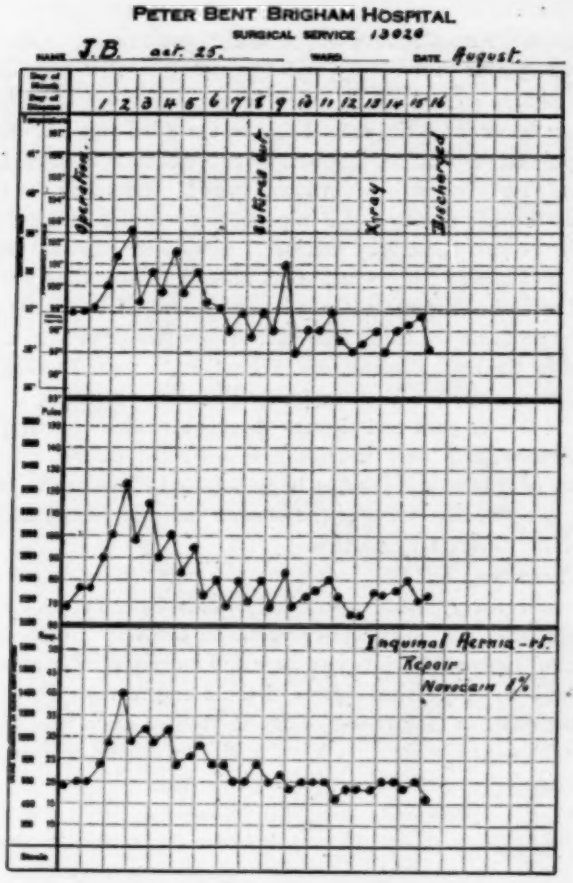


Fig. 1.—Case 1. Clinical chart.

chest showed small areas in both lungs in which there was slight dulness, increased voice sounds and a few râles with some increase in tactile fremitus. Within ten days these signs had all disappeared. Unfortunately no roentgen-ray studies were made until the twelfth day postoperative but even as late as that a subsiding bronchopneumonic process in the right lower lobe was demonstrable. Discharged well (Figs. 1 and 2).

This case was unusually severe. It is presented because of its immediate occurrence following operation. That emboli can actually take place during operation we feel satisfied and have known a patient to come out of the anesthetic with chest pain, a demonstrable friction rub and spitting up blood tinged sputum. The rough use of retractors surely could endanger a patient to this extent.

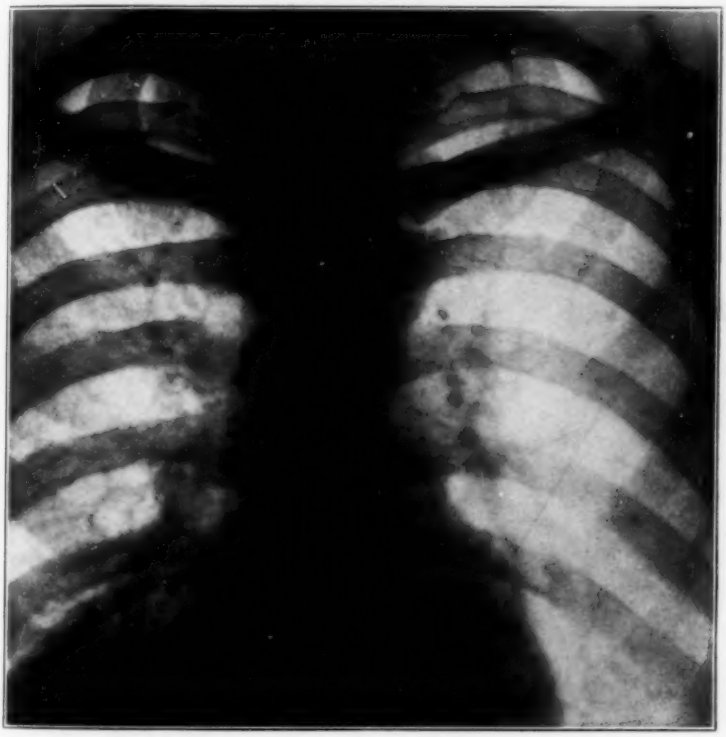


Fig. 2.—Case 1. Chest plate.

Case 2 (P. B. B. H. Surg. No. 13387).—A. H. McM., aged 33, married.

Diagnosis.—Varix femoral vein.

Operation.—Exploration, Oct. 16, 1920; ether; Dr. Homans. Convalescence normal until the eighth day after operation when the patient complained of a slight cough, and there was a beginning rise in pulse, temperature and respirations. Examination of the chest revealed a small patch of impaired resonance, bronchovesicular breathing and râles in the back on the left side below the angle of the scapula. Within ten days all these signs had subsided, but a roentgen-ray examination made on the seventeenth day after operation showed a spotty consolidation in the left upper and lower lobes. Discharged well (Figs. 3 and 4).

In this case, a sudden lesion appeared in a healthy young man eight days after a simple incision over the left femoral vein.

Case 3 (P. B. B. H. Surg. No. 13544).—D. D. B., aged 43, married. *Diagnosis.*—Duodenal ulcer.

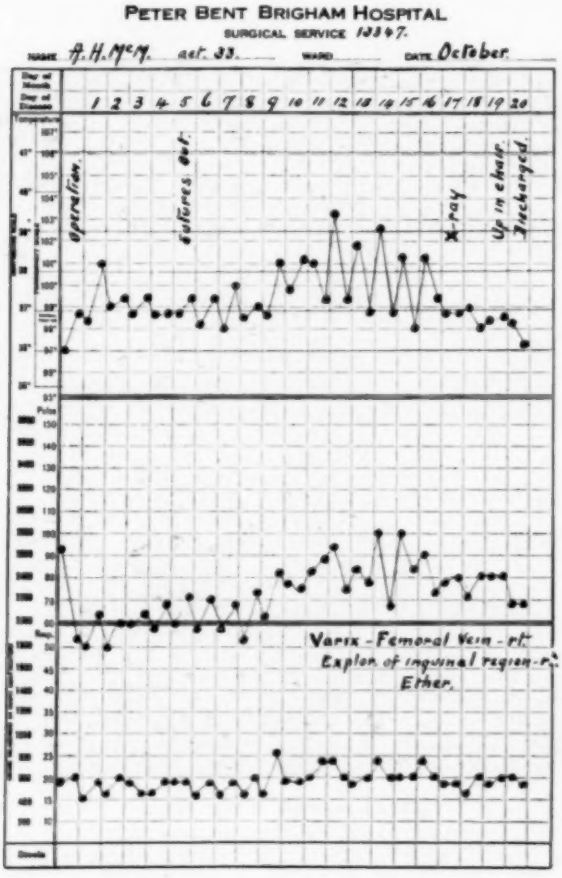

PETER BENT BRIGHAM HOSPITAL
SURGICAL SERVICE 1919 7.
NAME A. H. Mc M. aet. 33. WARD DATE October
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Operation
Sutures out.
X-ray
Up in chair.
Discharged.
Varix - Femoral Vein - rt.
Explon of inguinal region - rt.
Ether.

Fig. 3.—Case 2. Clinical chart.

Operation.—Cauterization of ulcer; posterior gastro-enterostomy, Nov. 22, 1920; gas-oxygen-ether; Dr. Cheever. Convalescence undisturbed until the eighth day after operation when the patient complained of pain in the right chest on breathing. Examination showed a friction rub, increased breath sounds and a few râles at the level of the angle of the right scapula. The temperature, respiration and pulse rate began to climb and all physical signs became more marked. There was no sputum. The leukocyte count rose to

15,000. On the eleventh day after operation a roentgen-ray examination showed a definite pneumonic process involving the middle and upper lobes on the right side. The entire picture cleared up in ten days (Figs. 5 and 6).

Case 4 (P. B. B. H. Surg. No. 12932).—E. A. H., aged 48, married.

Diagnosis.—Pyonephrosis in right kidney.

Operation.—Right nephrectomy, Aug. 13, 1920; gas-oxygen; Dr. Quinby. Convalescence uninterrupted until the fifth day postoperative when the patient complained of pain in the right lower chest. Examination of the lungs was

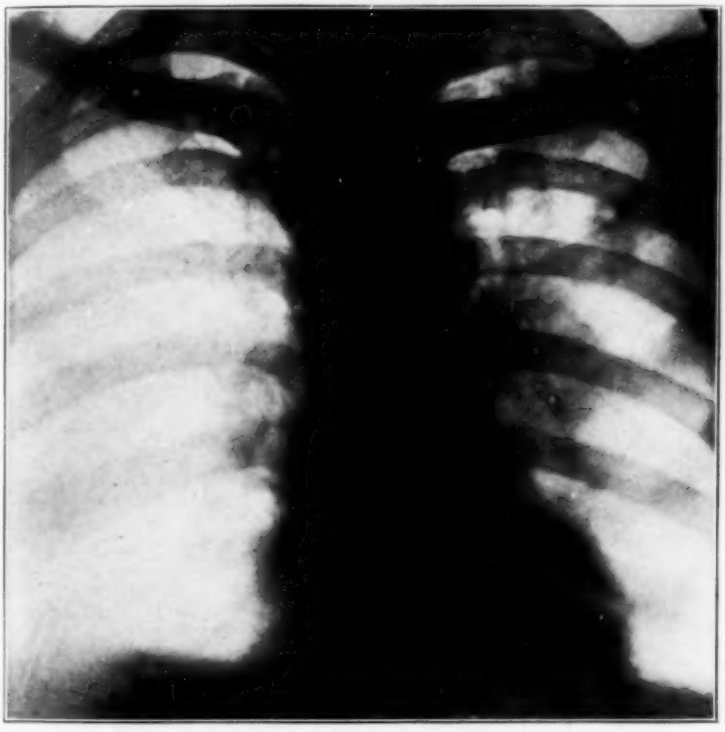


Fig. 4.—Case 2. Chest plate.

negative although there was a slight rise in pulse rate, temperature and respirations. Two days later auscultation revealed rather distant breath sounds and a questionable rub. There also was some limitation in the diaphragmatic excursion and diminished resonance. A roentgen-ray examination on the seventeenth day after operation revealed a resolving pneumonic patch involving the lower right lobe. From this time on improvement was rapid and the patient was free from symptoms and signs when discharged thirty days after operation (Figs. 7 and 8).

The explanation of why kidney operations sometimes result in pulmonary complications on the same side is not clear, except when there is direct extension of an infectious lesion, as when empyema occurs. Is

it possible that the manipulations on that side damage the lung somewhat so as to render it more susceptible to infarction? Or is it merely because pulmonary lesions usually involve the lower lobes? We have seen such complications in the opposite lung from the site of operation.

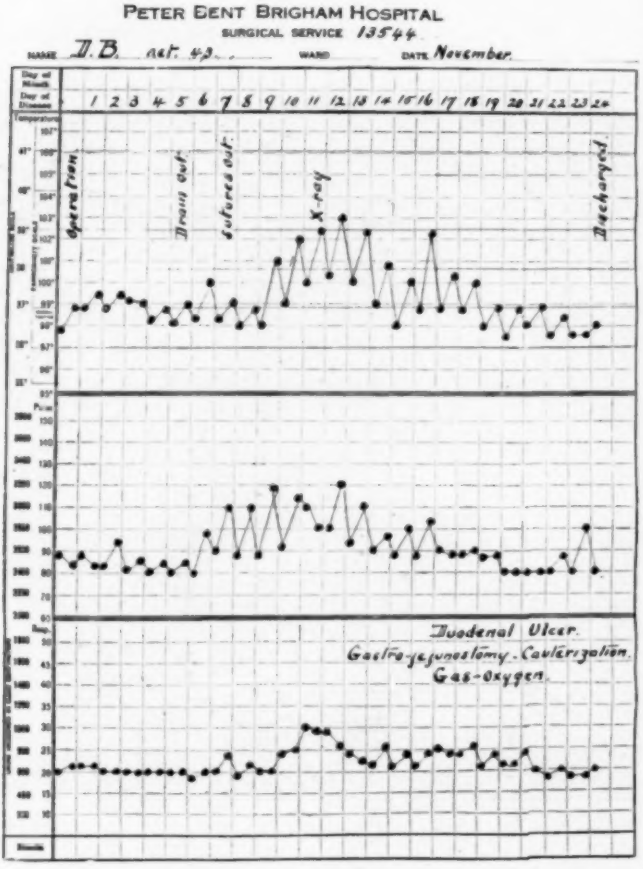

PETER BENT BRIGHAM HOSPITAL
SURGICAL SERVICE 13544
NAME J. B. ast. 43 WARD DATE November
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Operation
Drain out
Sutures out
X-ray
Discharged
Duodenal Ulcer.
Gastro-jejunostomy. Cauterization.
Gas-Oxygen.

Fig. 5.—Case 3. Clinical chart.

CASE 5 (P. B. B. H. Surg. No. 13363).—A. T. S., aged 23, single.

Diagnosis.—Acute appendicitis.

Operation.—Appendicectomy; no drainage, Oct. 18, 1920, ether, Dr. Jameson. Convalescence uninterrupted and unusually clear until the seventh day after operation when the patient complained of sudden severe pain in the right side of the chest and within a few hours he expectorated some bright blood-stained sputum. The temperature rose somewhat and respirations climbed markedly. Examination of the chest revealed a small patch behind the angle

of the scapula in which there were medium moist râles. No other signs were demonstrable and the whole picture subsided in three days. A roentgenogram made on the eleventh day after operation showed an increase in the shadow at the hilum on the right side and a little fluid at the base of the right lung. The patient was discharged well on the fifteenth day (Figs. 9 and 10).

This case presents a more ideal picture of this group as a whole than the preceding ones. All the cases, however, present different aspects, and include operations under the chief anesthetics.

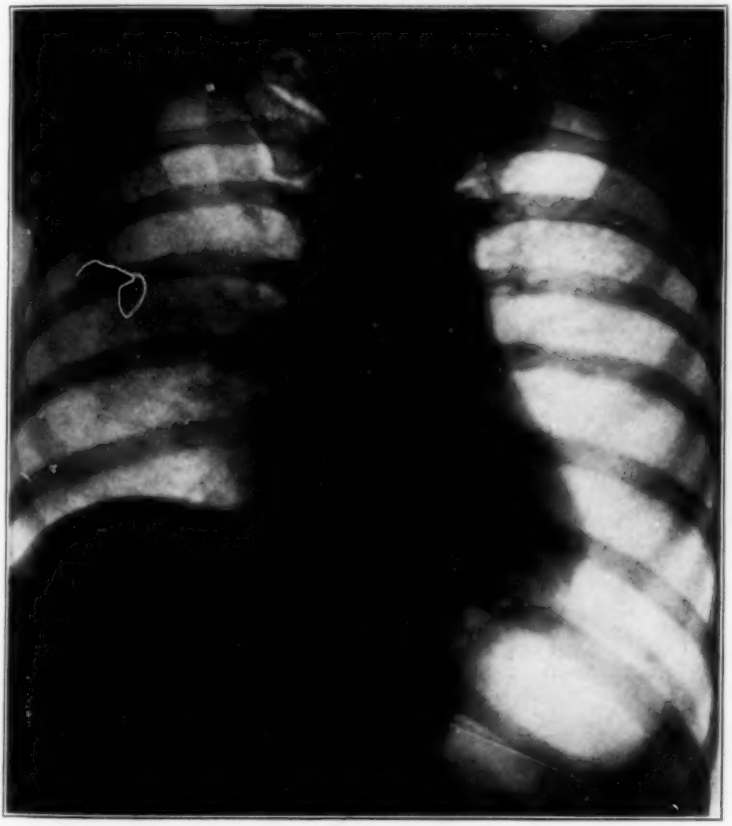


Fig. 6.—Case 3. Chest plate.

Pulmonary Embolism.—There are two fatal cases of pulmonary embolism in this year's series. A man, aged 67, operated on for prostatic hypertrophy, died on the third day after operation; a woman, aged 55, operated on for ulcer of the stomach, died on the twenty third day, three days after getting out of bed. A necropsy was held in both

cases, and the emboli were demonstrable in the pulmonary arteries. There is no need for any discussion concerning this frightful complication. We would, however, like to call to mind that granted that such large emboli occur, the mechanism for the manufacture of smaller ones must be the same and probably they occur with far greater frequency than in the large ones.

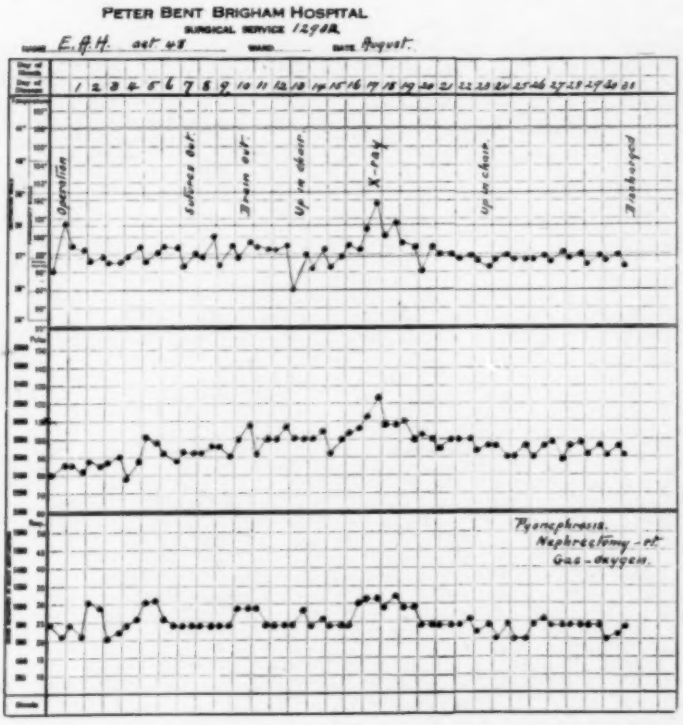


Fig. 7.—Case 4. Clinical chart.

DISCUSSION

The material presented would appear to indicate that a large proportion of postoperative pulmonary complications are caused by embolism from the operative field. This opinion, which we have previously attempted to substantiate [1b] is in agreement with a large proportion of the studies in this field.[73] It is, however, by no means generally accepted and curiously enough not by the anesthetists whom it attempts to defend! Preexistent pulmonary disease appears to be the

77. Consult introduction and review of the literature cited.

next most important factor. Such lesions are usually brought to activity through the irritation of an inhalation anesthetic and result in bronchitis or pneumonia. It is only in this type of case that the anesthesia has been proven at fault. The presence of sepsis in the operative field and the location of the operation are often important secondary factors. They do not, however, offer an explanation as to the mechanism by

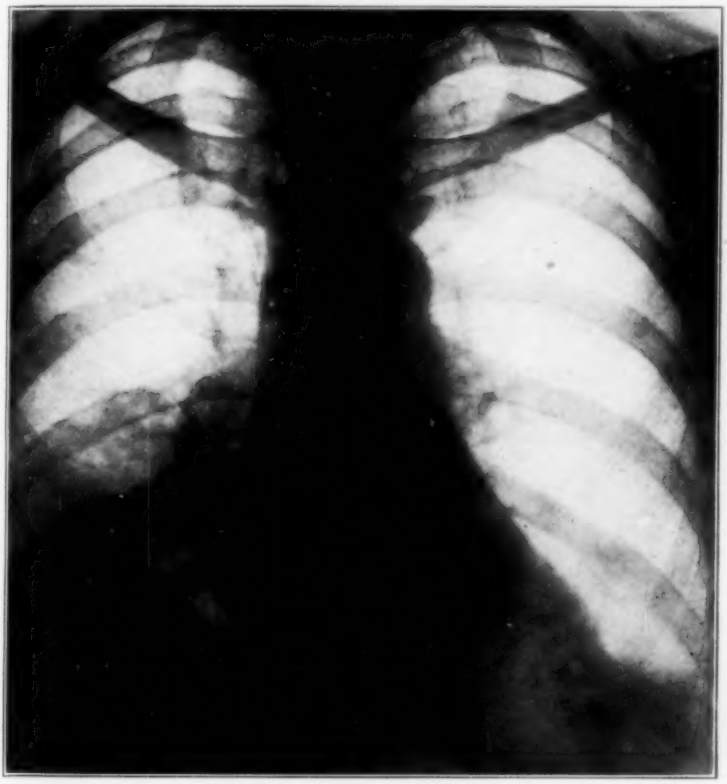


Fig. 8.—Case 4. Chest plate.

which the lung is injured. The further secondary factors of chilling, acidosis and seasonal incidence bear a varying relation in each case.

The arguments favoring embolism are: (1) the typical clinical picture, with sudden onset, focal signs, and, unless sepsis is present, rapid subsidence; (2) the fact that these complications occur frequently with local anesthesia; and (3) that they occur in a definite proportion according to anatomic divisions, these divisions being those kept in

greatest mobility and giving easy access by blood and lymphatic channels to the lung.[74] In favor of inhalation irritation is (1) the evidence that aspiration into the lung of the mouth contents does occur during anesthesia; (2) that Group IV pneumococcus, a common mouth inhab-

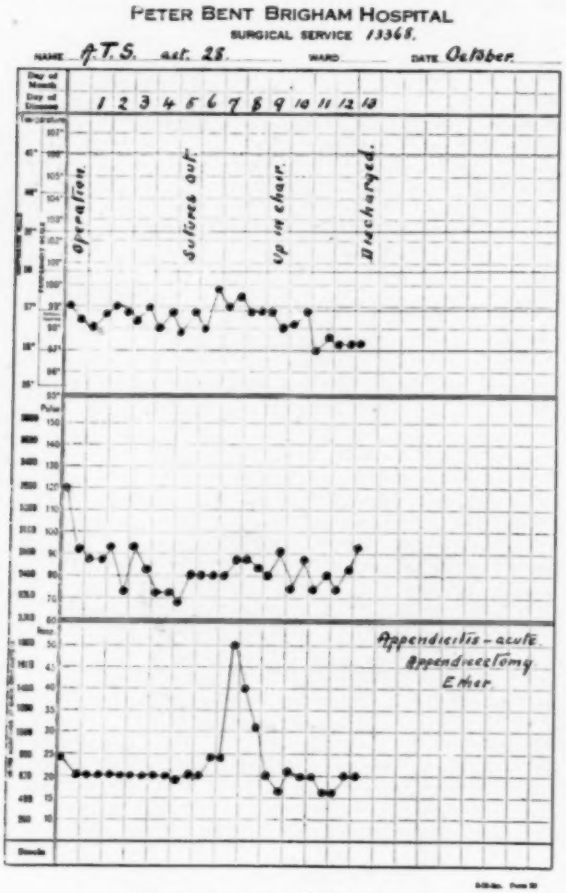


Fig. 9.—Case 5. Clinical chart.

itant, is most frequently found in these cases and (3) the many reports, including our own, that in certain cases with a pre-existing pulmonary disease inhalation anesthesia seems to have caused a flare-up of such a lesion.

74. Mandl, F.: Postoperative Lung Complications, Wien. klin. Wchnschr. **34**:214 (April 28) 1921.

Although under anesthesia the aspiration to the lung of mouth content undoubtedly occurs, there is no great proof that it effects any great pathology. All surgeons will recall execrable anesthesias with blue, coughing, vomiting patients. And yet, in how many such cases did pulmonary complication develop? If this were the chief factor, why is it that with the increasing perfection of the technic of anesthesia such complications continue to be found? And what is the explanation

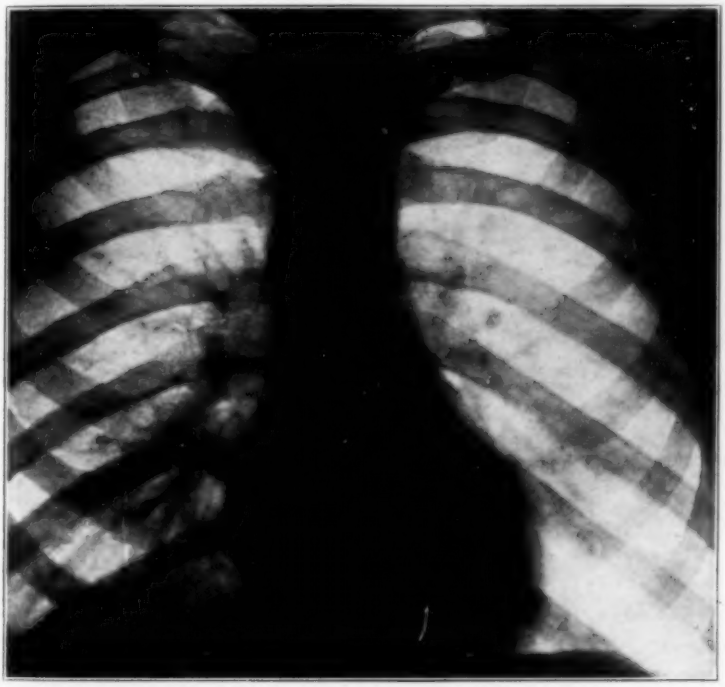


Fig. 10.—Case 5. Chest plate.

for those cases occurring with local anesthesia? That Group IV pneumococcus is found in the sputum in such cases is no proof that a true pneumonia has occurred for it has been shown that many normal mouths harbor this organism. Morever, the enormous volume of experimental pneumonia work does not reveal much success with inhalation infection except with doses so large that the conditions are not comparable to what might actually occur. Blake and Cecil's work on monkeys stands out almost alone, for the successful production of

pneumonia with small doses. Those who would blame inhalation anesthesia must bring more evidence to substantiate their hypothesis,

Of the sixty-three cases with complications reported in this series, only thirteen gave evidence of a pre-existing pulmonary lesion. Moreover, control roentgen-ray studies demonstrated that many persons with such lesions take inhalation anesthesia without any bad effects, whereas in more than 50 per cent. of the reported cases a typical picture of mild pulmonary infarction is presented.

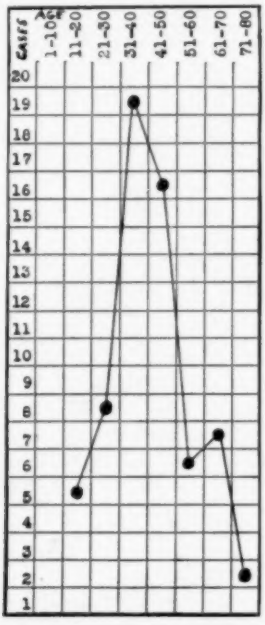


Fig. 11.—Incidence of postoperative pulmonary complications by decades.

Against the influence inhalation anesthesia may have in the production of these lesions are the facts, (1) that they occur equally when the anesthesia is in the most skillful hands; (2) that they occur with local anesthesia and, (3) that they occur in a greater relation to the mobility of the part than can be explained on any irritation hypothesis. With irritation, the presence of Group IV pneumococcus and a pre-existing pulmonary lesion one might expect a lobar distribution were this the true mechanism of these complications whereas lobar pneumonia proved to be a rare lesion in this study.

The part that the predisposing, accessory and secondary factors play is not clear. Chilling can be ruled out in a well ordered clinic.[75] The production of a real acidosis is still under dispute. If it does exist we might expect some lowering of the resistance to infection.[76] That the majority of the complications have occurred during the middle decade when individual resistance is at its best is not in keeping with this theory.

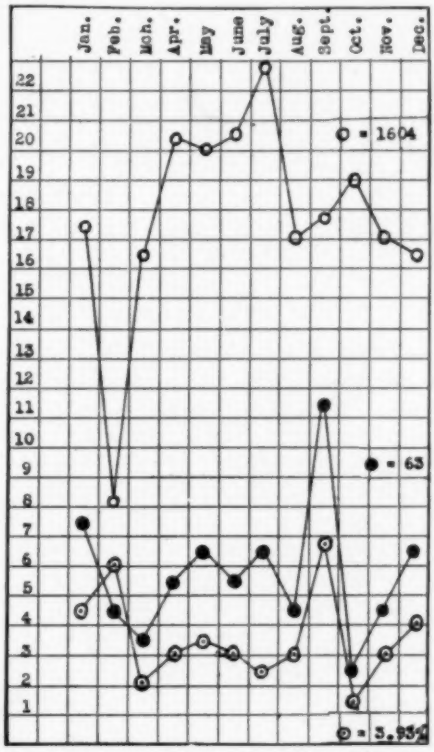


Fig. 12.—Seasonal variations in postoperative pulmonary complications: open circle, number of operations per month (the number at the side should be multiplied by 10); solid circle, number of pulmonary complications per month; circle and dot, percentage of pulmonary complications per month.

In a previous study [1b] the material presented demonstrated the great frequency of such complications with abdominal operations and the

75. Mandl [74] reports that during the winter 1919-1920 in Hochenegg's clinic in Vienna no coal was available and that the percentage of postoperative complications increased markedly. Such complications, however, do occur in the most luxuriously appointed clinics.

76. Hamburger, H. J.: Researches on Phagocytosis, Brit. M. J. **1**:37, 1916.

cases this year bear out the general comparison. The incidence in this restricted field has been so striking that there have been many excellent studies concerning it. Table 3 demonstrates the number of complications in relation to the field of operation.

TABLE 3.—Complications in Relation to Field of Operation

Operative Field	Lobar Pneumonia	Broncho-Pneumonia	Pulmonary infarction	Bronchitis	Pleurisy	Empyema	Pulmonary Embolism	Exacerbation of tuberculosis	Totals
Cranium	..	1	2	..	..	..	..	..	3
Breast	..	..	1	1	..	..	..	..	2
Kidney	..	1	2	2	..	..	..	..	5
Upper abdomen	..	1	4	5	1	1	1	..	13
Lower abdomen:									
1. General	..	3	3	..	..	1	.	1	8
2. Inguinal hernia	1	..	6	4	..	..	..	..	11
3. Pelvis	..	1	7	2	..	..	..	..	10
4. Bladder (prostate)	..	..	1	..	..	..	1	..	2
Perineum	..	..	1	..	..	..	..	..	1
Scrotum	..	..	..	1	..	..	..	..	1
Lower extremity	..	..	..	1	..	..	..	..	1
Varicose veins	..	..	3	..	..	..	..	..	3
Mouth	..	..	2	..	..	..	..	..	2
Neck	..	..	..	..	..	..	..	1	1
Total									63

This table demonstrates again that the preponderance of such complications follow abdominal operations. In this series forty-three of the sixty-three cases followed celiotomy (68 per cent.). Casually, it might not appear that infarction would be more common with abdominal operations and yet there are certainly several reasons favoring this. The anatomic studies of Sabin have demonstrated the free lymphatic drainage. But what of the blood supply? A large part of the intra-abdominal vascular tree drains to the portal system and must be excluded. The generally accepted higher incidence of such complications with epigastric lesions led us to believe that it was the incision in the abdominal wall itself which was most important, and the fact that this year two patients on whom an exploratory laparotomy was performed developed typical infarcts would seem to uphold this. The greater mobility of the parts due to respiratory movements is the direct cause for setting free the emboli, and the use of retractors, often used with great force in laparotomies, is an added danger. Furthermore, it has appeared that when great gentleness in traction was exerted and where perfect hemostasis and accurate closure was practised the incidence has been lessened. It is, however, quite possible, as we have previously indicated, that by the transfer of particles through the larger lymphatics pulmonary changes resulting in the signs of infarction occur. Mandl [74] reports that pulmonary complications in 1,379 laparotomies reached 14.5 per cent., whereas 1,585 operations elsewhere yielded 8.5 per cent. complications. These figures are higher than our own but are relatively the same.

PETER BENT BRIGHAM HOSPITAL
ANAESTHESIA CHART A

Name ..... Ward ..... Age ..... Date of Operation .....

Lungs ..... Heart .....

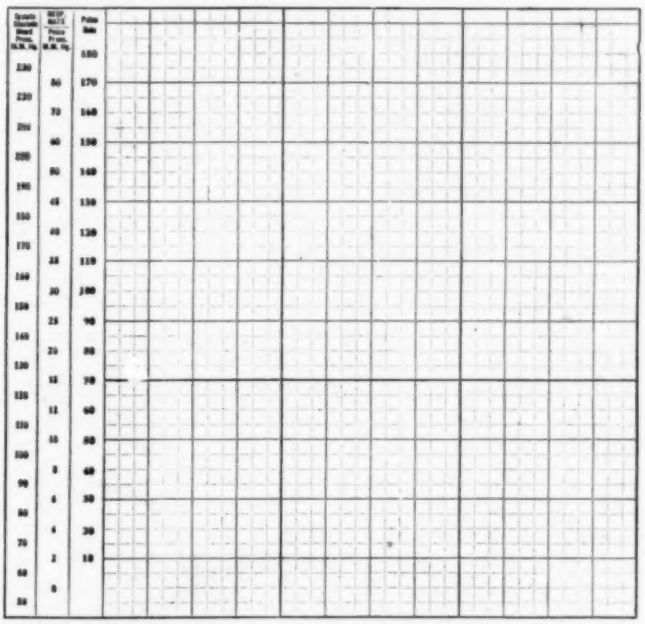
Urine ..... Blood Pressure ..... Rectal Temperature .....

Operator ..... 1st Assist ..... Peliminary Drugs .....

Operation ..... Anaesthetic ..... Amount .....

..... Method of Administration .....

Time of starting anaesth., beginning of op., removal of ahaesth., and close of op. to be recorded on chart.



CODE:—● PULSE RATE; ○ RESPIRATION RATE; V SYSTOLIC AND DIASTOLIC BLOOD PRESS; X PULSE PRESS.

Induction:—.....

Subsequent anaesthesia:—.....

.....

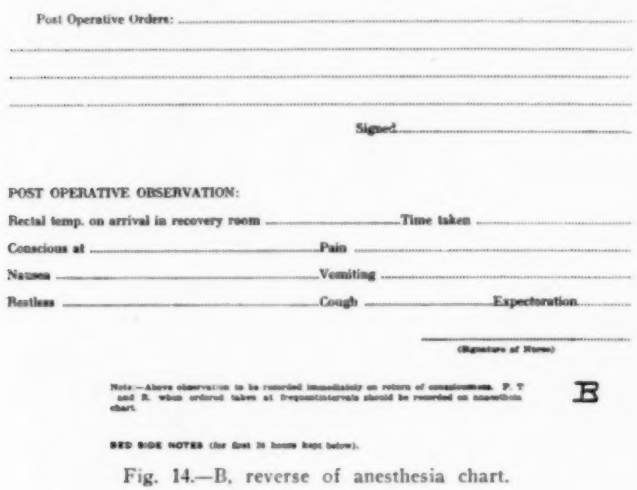
Condition on leaving operating room:—.....

.....

Drains ..... Anaesthetist .....

Fig. 13.—A, front of chart used to record progress of anesthesia.

In the material presented this year there are no cases in which we feel that aspiration or irritation due to the anesthetic was the chief causal element, except in those cases in which a pre-existing pulmonary lesion had been demonstrated. Thus, in the bronchitis and tuberculosis group there is no doubt that the inhalation anesthetic is to be blamed in many of the cases, but certainly not in all, for these complications also occurred with local anesthesia. And, moreover, a routine series of pre-operative and postoperative chest plates demonstrated the roentgen-ray evidence of pre-existing disease in which sometimes no change occurred after operation under inhalation anesthesia.



Post Operative Orders: .....

Signed .....

POST OPERATIVE OBSERVATION:

Rectal temp. on arrival in recovery room ..... Time taken .....

Conscious at ..... Pain .....

Nausea ..... Vomiting .....

Restless ..... Cough ..... Expectoration .....

(Signature of Nurse)

Note.—Above observation to be recorded immediately on return of consciousness. P. T and R. when ordered taken at frequent intervals should be recorded on reverse side of chart.

B

BED SIDE NOTES (for first 24 hours kept below).

Fig. 14.—B, reverse of anesthesia chart.

Through the successive years during which we have been interested in this subject the roentgen ray has steadily proved an increasingly valuable and reliable adjunct to accurate diagnosis. The opportunities to put it to more extensive use during 1920 have not only enabled us to make more accurate diagnoses and to pick up doubtful cases but have given us a greater insight into pulmonary conditions and, in particular, the frequency, type and reaction to inhalation anesthesia of such pre-existing foci of pulmonary disease. These studies have proved to our satisfaction that without such controls the classification and study of these complications is difficult and incomplete.

A study of the distribution of the complications resulting from infarction, embolism and pneumonia, shows twenty-five situated in the base of the right lung, eleven in the base of the left lung and six bilateral. If the lesions were irritative and infectious, it is unusual

that involvement of the upper lobes never occurred. Welch states that pulmonary infarction is most common in the lower lobes, more frequently right than left.

Figure 11 demonstrates the incidence of pulmonary complications by decades. Figure 12 shows the seasonal variations and Table 4 shows the types of complications in relation to the various anesthetics. There is little to be said about any of these findings. Obviously the majority of complications occur in the fourth decade as the majority of patients are that age. It should be remembered that pneumonias of either type are more frequent in the first two decades and the fifth decade (Osler and Macrae [77]). The seasonal chart shows no striking segregation in relation to climatic conditions. Table 4 shows that about one half as many cases received gas-oxygen as ether. This alone, however, is not convincing since obviously those with pre-existing pul-

TABLE 4.—Anesthetics Used in Various Complications

Complications	Ether	Gas-Oxygen and Ether	Gas-Oxygen	Procain	Totals
Lobar pneumonia	0	0	0	1	1
Bronchopneumonia	4	1	2	0	7
Bronchitis	11	0	5	0	16
Exacerbation of tuberculosis	1	0	1	0	2
Pleurisy	0	0	2	0	2
Empyema	1	0	0	0	1
Infarction	24	0	7	1	32
Pulmonary embolism	0	0	2	0	2
Totals	41	1	19	2	63

monary signs were usually given gas-oxygen. That only two complications occurred with procain is exceptional although not far from proportionate to the total use of this anesthetic in this clinic and the fact that local anesthesia is rarely used in abdominal operations excludes this added predisposing factor in the local anesthesia cases reported. Of the total 1,604 operations, 875 were performed under ether, 546 under gas-oxygen, 179 under procain, 2 under chloroform and in two cases no anesthesia was used. The morbidity percentage is 4.6 per cent. for ether, 3.5 per cent. for gas-oxygen and 1.1 per cent. for procain.

The difficulties of assembling accurate data have been somewhat mitigated by the use of the chart shown in Figures 13 and 14 which is reproduced in the hope that the few clinics which have not as yet adopted some such form may be led to use one. We have found the data contained on this chart of the greatest value—(1) in ensuring a careful anesthesia, and (2) for all kinds of follow-up work and case studies. It has the great value of providing the anesthetists with sufficient work so that their attention is never side-tracked to the operation or to other activities in their proximity.

77. Osler, W., and Macrae, T.: Lobar Pneumonia, Mod. Med. **1**:202, 1913.

As a further postoperative protection all patients are kept on the operating room floor, in separate recovery rooms and under constant observation until fully conscious. This does away with the possible danger which may come from transporting unconscious patients through draughty corridors and from the more active risk of reaching a short-handed ward where they cannot be under constant observation during the period of recovery.

The condition known as massive collapse of the lung first described by Sir John Bradford [78] has recently through the papers of Scrimger [79] been brought into the category of postoperative pulmonary complications. In Scrimger's last paper he reports seven such cases in 540 operations. The routine anesthetic of chloroform-ether is used. His patients soon after operation developed sudden respiratory distress, pain and cough. Roentgen-ray studies revealed marked displacement of the heart to the affected side. Recovery usually occurred within twenty-four hours. The etiology of this condition is not known, possibly it is due to inhibition of the diaphragm or to vagal influences causing contraction of the muscular elements of the lung. Mortimer [80] places great stress on respiratory movements and states that the lower lobes may collapse when movements of the diaphragm are restricted either by pain or bandages. This condition deserves greater study and necessitates control roentgenograms. It has not been observed in this clinic.[81]

SUMMARY AND CONCLUSIONS

Postoperative pulmonary complications are due in the majority of cases to embolism from the operative field. The result is pulmonary infarction or fatal pulmonary embolism. The latter is a rapidly fatal, well recognized clinical picture. The former is caused by the transmission to the lung of a small thrombus or many thrombi with resultant characteristic clinical picture. This consists of sudden pain, expectoration, often blood tinged, the elevation of respiration and pulse rates and temperature, and the signs of a focal consolidation often overlaid by a friction rub. These patches are demonstrable by the roentgen ray, provided such studies are made at once. There usually follows rapid defervescence and the subsidence of all symptoms within a week.

---

78. Bradford, Sir J. R.: Massive Collapse of the Lung, Oxford Medicine, New York, and Oxford University Press **2**:127, 1920.

79. Scrimger, F. A. C.: Postoperative Massive Collapse of the Lung, Surg., Gynec. & Obst. **32**:486, 1921.

80. Mortimer, J. D.: Med. Press & Circ. **108**:505, 1919.

81. Schultze, E. C.: A Report of Twenty-Seven Cases of Pneumonia Following the Inhalation of Ether and Chloroform, Med. & Surg. Rep. Presbyterian Hospital, N. Y. (Jan.) 1898, p. 311.

The causes of infarction are (1) trauma; (2) the mobility of the part; (3) sepsis. The prognosis in this group is excellent.

Irritation and aspiration due to inhalation anesthesia may be the cause of a small percentage of postoperative pulmonary complications. These usually fall into the bronchitis or pneumonia groups. Inhalation anesthesia rarely results in such lesions unless there is present a pre-existing pulmonary disease such as a chronic bronchitis, incipient tuberculosis or a definite tendency towards pulmonary disease.

The fact that these complications occur with local anesthesia, with inhalation anesthesia in the most expert hands and in a definite relation to the mobility of the operative field is taken as evidence against the importance of the irritation of inhalation anesthesia in the production of these lesions.

Anesthetists and anesthesia should not bear the blame for these complications.

There is as yet no proof or evidence that chilling or acidosis plays any appreciable rôle in this field.

A reduction in the number of cases that result in these complications can be had by (1) a reduction in trauma at operation; (2) accurate hemostasis; (3) the careful control of sepsis and (4) the use of great caution in operating upon patients who have demonstrable pulmonary disease. A high fluid intake and all general precautions giving assistance to the circulatory apparatus will be of definite value once such complications are established.

We are greatly indebted to Dr. Lawrence Reynolds, roentgenologist of the Peter Bent Brigham Hospital, for his excellent plates, fluoroscopic studies and cooperation.

THE PATHOLOGY OF CIRRHOSIS OF THE LIVER

AN HISTORIC-PATHOLOGIC STUDY

FREDERICK EPPLEN, M.D.
SPOKANE, WASH.

Cirrhosis of the liver is a chronic, recurring, probably focal, possibly diffuse degeneration or necrosis of the parenchymatous cells of the liver, modified by concurrent and intercurrent periods of regenerative proliferation of the parenchyma, with connective tissue replacement of destroyed areas. Acceptance of this definition and any concept that cirrhosis of the liver is a disease entity are incompatible. The granular liver, with its associated splenic tumor and portal stasis, is as surely a consequence of some preceding disease as the cyanotic induration of the liver and lungs and edema are the consequences of chronic valvular heart disease. That disease is the degeneration or necrosis of the liver cells, a process, the clinical manifestations of which are as yet unknown.

The question arises: Are we concerned with a single disease resulting in this picture, or are there many entirely different processes which eventuate in the same ultimate anatomic picture? Further, and perhaps more important, is the question whether the primary disease has its seat in the liver, or whether that organ is involved only secondarily or in association with some other organ, as for example, the spleen. The varying clinical pictures under which cirrhosis may manifest itself, particularly with reference to its onset, and still more, its etiology, makes it seem reasonable to assume that the end-result called cirrhosis of the liver can be produced by a variety of primary clinical processes. Accepting its association with other diseases, the second question may be reasonably assumed to be correctly answered when it is stated that it may be primary in the liver or may be secondary to (or associated with) disease in some other organ. Of course, this statement might, with equal accuracy, be made the other way around, namely, that this pathologic picture may exist alone or it may produce lesions in other organs. Perhaps, both are true. For example, it might be secondary to changes in the spleen in Banti's disease, while the brain lesion in Wilson's disease might be dependent on the liver pathology.

ETIOLOGY

The intimate relationship of the etiology and pathogenesis of cirrhosis is sufficient reason for a brief resumé of the usual etiologic factors concerned in Laennec's cirrhosis, especially since this relationship is here particularly interesting and apparently insoluble.

The term "alcoholic cirrhosis" applied so universally to the hobnail liver characteristic of Laennec's cirrhosis is not altogether justifiable. Alcohol is undoubtedly closely associated etiologically with the great majority of cases; and that alcohol alone can produce the disease has apparently been proved experimentally by many workers. Grover [1] published the most recent work on experimental alcoholic cirrhosis, and has made an admirable collection of the literature. He concludes that alcohol given to experimental animals over a long period of time can produce a degeneration of liver cells followed by connective tissue proliferation. He concedes that other processes may be associated, but, if so, their nature is so obscure that their modus operandi is not known. Saltykow [2] produced cirrhosis of the liver by injecting alcohol into the ear vein of rabbits. Fahr [3] and Schäfer [4] were successful in similar experiments. Kyrle and Schopper [5] produced parenchymatous changes and fatty degeneration in all cases of repeated introduction of alcohol by intravenous, subcutaneous and gastric routes. In seven cases there was necrosis of portions of the lobule and replacement fibrosis; in fourteen cases there was round-cell infiltration in the portal fields, and in seven others, there was connective tissue proliferation with bile duct formation. The livers of three rabbits showed typical Laennec's cirrhosis.

Not all workers, however, were able to produce cirrhosis in experimental animals. Pogenpohl,[6] Klopstock,[7] von Baumgarten [8] and Bischoff [9] were notably unsuccessful. All agreed, however, that alcohol was productive of extensive fatty degeneration.

Lancereaux,[10] who studied the etiology of cirrhosis of the liver for many years, concluded that cirrhosis could be produced by substances used as preservatives and to give certain wines an especially "dry" flavor. He had particular reference to potassium bisulphate with which salt he was able to produce Laennec's cirrhosis by feeding it to animals.

MacCallum, in his last textbook (1916), is very emphatic that it has not been demonstrated experimentally that alcohol produces cirrhosis. If a large number of chronic alcohol addicts be studied, only a very few will be found to suffer from cirrhosis. He states that all sorts of degenerations may take place, both in experimental alcoholism

1. Grover: Arch. Int. Med. **17**:193 (Feb.) 1916.
2. Saltykow: Verhandl. d. deutsch. patholog. Gesellsch. **15**:228, 1910; Zentralbl. f. allg. Path. u. path. Anat. **22**: 1910.
3. Fahr: Virchows Arch. f. path. Anat. **217**:397, 1911.
4. Schäfer: Virchows Arch. f. path. Anat. **215**: 1913.
5. Kyrle and Schopper: Virchows Arch. f. path. Anat. **215**:359, 1913.
6. Pogenpohl: Virchows Arch. f. path. Anat. **116**:466, 1909.
7. Klopstock: Berl. klin. Wchnschr. **47**:1532, 1910.
8. Von Baumgarten: Verhandl. d. Deutsch. path. Gesell., 1907.
9. Bischoff: Ztschr. f. Exper. Path. u. Therap. **11**:445, 1912.
10. Lancereaux: Bull. de l'Acad. de méd. Par. **74**:15, 1910.

in animals and overindulgence in man. Since MacCallum has been one of the particularly deep students of cirrhosis, his statements are of especial value. He calls attention to the work of Longcope, who has produced changes very closely resembling cirrhosis of the liver by the injection of proteins and by other experiments suggesting some form of protein sensitization or intoxication as the best explanation. MacCallum's ultimate conclusions are, that what we see as cirrhosis at the necropsy table is scar tissue and efforts at regeneration and that there are many processes which can lead to them.

These observations greatly accentuate the difficulty of establishing a clear-cut pathogenesis, particularly if one tries to accept the theory that cirrhosis of the liver is essentially secondary to some toxic process in the portal zone.

There are, however, so many etiologic factors other than alcoholism operative that this is only the beginning of confusion. Warthin recently, before the Portland Academy of Medicine, expressed the belief that some day it would or might be proved that cirrhosis was the result of the joint action of syphilis and alcohol. At that time he stated that he had demonstrated *Spirochaetae pallidae* in two such livers examined. Syphilis as an etiologic factor was the subject of a recent paper by Symmers.[11]

Malaria is immediately suspected in malarial districts. This may be a relic of the days of pure empiric medicine; the enlarged spleen of both diseases furnishing the empiric resemblance. However, malaria has not yet been entirely swept from the paragraphs on etiology, even in relatively recent articles.

The outstanding objection to alcoholism as the only etiologic factor is that we see so many cases in which there is not the slightest suspicion of alcoholic abuse. Indeed, the patient from whom the liver presented was taken, was a total abstainer, and so it is in many other case histories. It will be interesting to note whether the present prohibition law will cause this disease to diminish, or whether, in the perversity of things, the illicit brews and distillations, at present so frequently heard of, will actually continue to be a factor. Perhaps, their vicious nature and impurities will lead to a greater morbidity with reference to cirrhosis among drinkers than ever before.

Recently Miller,[12] in discussing this question, published figures which show a definite decrease in the admission of cases of cirrhosis of the liver to Cook County Hospital since prohibition went into effect July 1, 1919. He feels, however, that some of the reduction in the number of cases admitted to the hospital may have been due to the influenza epidemic raging at that time, during which the hospital was

11. Symmers: Internat. Clin. **1**:58, 1917.
12. Miller: J. A. M. A. **76**:1646 (June 19) 1921.

closed to all but acute cases. More time must elapse and illicit vending be better controlled before the effect of prohibition can be estimated accurately.

It is possible that a particular type or degree of gastro-enteritis must be produced by alcoholism before cirrhosis can develop. On this basis we can also explain those cases in which alcohol was not indulged in, on the assumption that an identical or very similar gastro-enteritis is produced by other etiologic factors, for example, the custom of pepper and curry eating in India. Cirrhosis then follows as it does after that of alcoholism. It does not, however, explain those cases of experimental cirrhosis in which alcohol was administered subcutaneously and intravenously.

As in all chronic degenerative diseases, infection is being spoken of more and more in recent literature as a possible etiologic factor in cirrhosis, and there is much to commend this hypothesis. In searching the literature we found this etiology mentioned by Raoul Gaston [13] as early as 1893. He believed that he had established an infectious origin for some cases which followed prolonged infectious diseases. His interpretation was that an inflammatory infiltration had occurred about the radicals of the portal vein, and thus precipitated the disease. It is to be noted that at that time the disease was believed to be primary in the connective tissue.

The etiology of no chronic degenerative disease would be complete unless some mention be made of chronic metabolic or digestive toxicoses. They are visionary, indeed, and yet possess an alluring appeal in so many diseases, and especially in connection with cirrhosis, that they cannot be dismissed entirely, theoretical though they be at present. Particularly appealing is the assumption that the poison responsible for this disease may be produced in the spleen.

Tabulate the clinical types of Laennec's cirrhosis and the all-comprising single etiologic factor at once disappears.

1. *Laennec's Cirrhosis in Topers.*—These are so predominant in numbers that alcohol becomes overwhelmingly the greatest single factor.

2. *Laennec's Cirrhosis, Where Alcoholism Clearly Was Not a Factor.*—The etiology of these cases is entirely unknown. They are not so rare as is generally assumed, and are most common in women and children.

3. *Banti's Disease.*—By definition Banti described this as a certain type of anaemia, plus Laennec's cirrhosis and splenomegaly in which the etiology must be unknown. If the victim of this disease is a chronic alcoholic Banti's disease may not be used as a designation.

13. Gaston, Raoul: Thésé de Par., Du Foie Infectieux, Paris, 1893.

4. *Diabète Bronzé; Cirrhose Pigmentaire.*—Clearly this is a definite clinical entity. It is perhaps an event in the course of some other disease, but for that matter the same may be said of Banti's disease.

5. *Progressive Lenticular Degeneration* (commonly called Wilson's disease [14]). Here we have a rare familial nervous disease occurring during the years of adolescence in individuals who are not addicted to alcoholic excess, frequently not even to occasional indulgence. The etiology is entirely unknown.

Cirrhosis is occasionally found by surgeons unrelated to the condition which called for the operation and apparently of no immediate clinical importance.[15] So, too, it is often accidentally found at necropsy, apparently not the cause of death nor even contributory. However, some caution should be exercised in brushing aside a cirrhosis of the liver as an "accidental finding" at necropsy. This is exactly what occurred in the first case of progressive lenticular degeneration found at necropsy at the National Hospital for the Paralyzed and Epileptic in London, only to be resurrected from the archives years later by Wilson, who then properly classified it and placed it in his series reported in Brain in 1912. Howard and Royce [16] narrowly missed making the same mistake in their case. It is just this association with other apparently more important anatomic findings that makes such "accidentally" found cirrhoses interesting and at the same time extremely puzzling.

PATHOGENESIS

The older theories located the origin of the disease in the connective tissue stroma, a chronic interstitial hepatitis. Assuming that the disease was more or less acute in its earlier stages, and that all acute inflammatory processes are associated with edema and hyperemia, the swollen liver of early cases was thus readily explained. As the disease progressed it became more chronic, hence more productive and the cellular elements of the connective tissue proliferated, sooner or later insinuating themselves between the liver cells in the lobule, gradually snaring them off. As the new tissue acquired age it began to contract, reducing the size of the liver simultaneously by contraction and by pinching the liver cells to death, lessened parenchyma meaning lesser volume. In younger individuals the snaring process was likely to take larger bites of tissue, while in older individuals small areas would be surrounded, so the theory stated. Hence we had multilobular and unilobular cirrhoses, both terms now very little used, the former being reserved by some writers for the end-result of syphilitic hepatitis in children.

---

14. Wilson: Brain **34**:295, 1912.
15. Mayo: J. A. M. A. **70**:136 (May 11) 1918.
16. Howard and Royce: Arch. Int. Med. **24**:497 (Nov. 15) 1919.

This theory of the pathogenesis of the disease did not take into consideration the incongruity of assuming a special connective tissue vulnerability in the liver as compared with that of other parenchymatous organs. No other organ was known to suffer an inflammatory disease in its supporting structures with secondary destruction of the parenchyma. Indeed, it is a well known law that a tissue is vulnerable in direct proportion to its specialization.

Furthermore, pathologists of that day did not understand the regenerative powers of parenchymatous organs and particularly those of the liver. Ponfick [17] was the first pathologist to experiment on the regenerative power of the liver. He found that as much as four-fifths of the liver of dogs could be removed with subsequent regeneration to normal size. Considering that the liver normally has an enormous surplus of tissue as a margin of safety, its regenerative power after experimental extirpations is but another manifestation of its marvelously large margin of safety.

In 1894, Marchand [18] reported a case of acute yellow atrophy terminating in "multiple nodular hyperplasia." The patient, a woman, aged 28, was brought to the hospital moribund, therefore an accurate history was not available. It was ascertained, however, that she had had "catarrhal jaundice" for several months, during part of which time she had a swollen abdomen and legs, and that in the last few days she had become suddenly and seriously ill. The skin was yellowish and there were some small ecchymoses in the conjunctiva.

At the necropsy the liver was found greatly reduced in size, with a hobnail surface, the eminences ranging in size from that of a pea to a cherry. The elevated areas were pale reddish yellow in color, the depressions dark red. On cut section areas of yellowish liver tissue were seen with a reddish structure intervening and predominating, the former elevated, the latter depressed. Acinus markings were not to be seen in the nodules. Marchand gives a critical analysis of the pathologic anatomy and histology of this liver, reaching the conclusion that the process could not be a cirrhosis, because of the nature of the dark red structure between the nodules of liver cells, a technical study that must be read in the original to be appreciated. His conclusion was that he had before him "a liver presenting changes which can leave no doubt that we are dealing with the residua or results of a so-called acute yellow atrophy." He mentions a similar case published by Klebs, which "showed anatomically in extenso the picture of a typical red atrophy of the liver whereas the clinical course of the disease had been that of a chronic, possibly recurrent type of the disease."

17. Ponfick, quoted by Kretz: Verhandl. d. Deutsch. path. Gesellsch. **8**
18. Marchand: Beitr. z. path. Anat. u. z. allg. Path. **17**: 1894.

Marchand's concluding paragraph freely translated, states that we have

> the very unusual example of a yellow atrophic liver which has reached an unusually high degree of regeneration, or better still, reproduction. It is not unlikely that under more favorable circumstances a greater development of regenerative changes could have occurred; never, however, could complete regeneration of structure be attained. If we could imagine the regeneration I have described still further advanced, we would then have the picture of a large lobule cirrhosis of the liver such as we see in childhood.

Meder,[19] his assistant, published six or seven cases very closely resembling Marchand's. MacCallum[20] reports similar changes of a reproductive nature occurring after acute yellow atrophy.[20a]

Kretz[21] was the first to coordinate these facts, namely, the regenerative changes in the liver, as ascertained by Ponfick experimentally and by Marchand pathologically, and the close resemblance of Marchand's and similar cases of the end stages of acute yellow atrophy, on the one hand, with fully developed cirrhosis of the liver on the other. He enunciated the present day conception of the pathogenesis of cirrhosis of the liver, for which MacCallum,[22] the greatest American student of cirrhosis, gives him full credit. Yet Ackerman[23] was the first to express the belief that the disease was primarily a parenchymatous process.

The primary process in cirrhosis of the liver is a parenchymatous change as in actue yellow atrophy, but not so rapid; slowly the parenchyma is destroyed—a little today, a little more tomorrow—inumerable minimal attacks, continuing from onset to termination, with periods of quiescence intervening. While the degeneration and necrosis of cells is progressing, regenerative mitoses are occurring concurrently, at first only among the liver cells, but later the biliary ducts, genetically closely related to liver cells, partake in the effort to replace destroyed liver cells by metaplasia, perhaps after the regenerative powers of the liver cells have become exhausted or cannot maintain the pace set by the advancing disease. Periods of complete quiescence may result in restitution to nearly normal liver sufficiency. Alternating periods of progress

---

19. Meder: Beitr. z. path. Anat. u. z. allg. Path. **17**: 1894.

20. MacCallum: Johns Hopkins Hosp. Rep. **10**: 1903.

20a. Since this paper was submitted for publication, I found a liver of this type at necropsy in the body of a young man, aged 22. Briefly, the clinical history was that he had had jaundice for five years, which was associated with ascites and edema, marked weakness and frequent bowel movements. The mode of onset could not be determined definitely but was more or less acute. The clinical diagnosis had been chronic pancreatitis. At necropsy a nodular, hyperplastic liver was found. The immediate cause of death was a terminal peritonitis. The case will be reported in full later.

21. Kretz: Wien. klin. Wchnschr. **13**: 1900; u. Ergb. d. allg. Path. **8**: 1904.

22. MacCallum: J. A. M. A. **43**:480 (Sept. 3) 1904.

23. Ackerman: Virchows Arch. f. path. Anat. **115**.

and quiescence may continue for years until finally the patient succumbs or, perhaps, in rare cases the disease may become permanently quiescent while the liver is still capable of meeting the metabolic needs of the individual.

So it is that the parenchyma dies and is replaced by connective tissue, new parenchyma replaces the old and is again destroyed to be replaced by other new parenchyma; constant repetition of destruction and regeneration resulting in a completely rebuilt liver. In advanced cases not the slightest vestige of the original tissue remains; even the circulatory system has been rebuilt.

If we are ever permitted to use comparisons and analogies, it seems justifiable here. So we may think of cirrhosis of the liver as the result of minute attacks of something closely resembling acute yellow atrophy, at least in the nature of its action. Acute yellow atrophy is no more a definite clinical entity than is Laennec's cirrhosis; both may be produced by a variety of causes. One should think of the two diseases as being analogous, one acute, the other chronic, differing only slightly in the nature of the pathologic process, but very markedly in degree. One is always acute and nearly always fatal; the other is chronic and likewise nearly always fatal. Occasionally the patient lives long enough after an attack of acute yellow atrophy to produce regenerative phenomena of sufficient degree to make the liver closely resemble that of the chronic process, in which the patient always lives long enough to excite regeneration.

The origin of the new or regenerated cells appearing in the nodules is manifestly from the surviving liver cells assisted by the bile ducts. The objection sometimes raised that it would be impossible for cells to regenerate in the presence of a circulating noxious agent capable of destroying mature cells is scarcely valid. There are many known instances of such occurrences. The further objection to this belief, that we do not see partially destroyed cells, is not true. We do see them, rarely it is true, but this is a very chronic disease; cellular death is hastened but not to a degree to be a predominating feature easily found in any given slide. The same may be said of another objection sometimes made, that we do not see mitoses. We do see them occasionally, especially early. MacCallum [22] answers this argument by referring to the differences in acute and chronic nephritis. Mitoses are seen in acute nephritis relatively frequently. Regenerative changes are perfectly evident macroscopically and are generally accepted in chronic nephritis but they are not sufficiently in evidence to be discovered microscopically. They are found only in acute cases or acute exacerbations.

This comparison of acute yellow atrophy and cirrhosis at once brings two diseases of obscure origin into close relationship clinically;

indeed, their behavior is often quite similar, except in the matter of time. It serves the further purpose of making the pathogenesis of the chronic form of the two diseases, cirrhosis, quite clear.

MINUTE ANATOMY OF LIVER

As a prerequisite for an understanding of the architecture of the cirrhotic liver, a clear conception of its normal architecture is essential.

Early in intra-uterine life the liver consists of two dense meshworks of capillaries derived from the portal vein and hepatic artery converging into the hepatic vein, within which are embedded the liver cells. Essentially the liver is a radiation of two sets of capillaries arising from a common point, the portal fissure, converging into a second common point, the hepatic vein. Since the liver is usually regarded embryologically as an epithelial bud arising from the primitive foregut, therefore essentially an epithelial structure, an adequate conception of its complicated vascular architecture cannot be obtained. Indeed, it is just this that leads to the usual misconception of the anatomy of the lobule or acinus, described as it is, as a rounded or polyhedral mass of radiating cells with a central vein, surrounded by a connective tissue capsule. There are actually no such glandular lobules in the liver each separate and distinct from its neighbor. The liver is essentially a vascular skeleton in the interstices of which is a mass of cells, just like the flesh on a skeleton. Hence, all parts of the liver tissue are not only in contiguity but in direct continuity with all other parts without complete connective tissue separation or segregation into lobules.

The efferent blood flows into the ultimate hepatic vein through its various collaterals, these branches collecting the blood from different parts of the liver by a system of "continental divides" which makes the separation into lobules or acini as we must understand them. These "continental divides" between acini are theoretically hard and fast divisions but histologically and physiologically they are neither visible nor demonstrable, in fact, they may vary with physiologic necessities. At various points this parenchymatous mass or theoretical lobule is penetrated by branches of the portal vein and hepatic artery, clothed by a thin coat of connective tissue in which are also enclosed the bile ducts. It is the multitudinous, almost ubiquitous, ramifications of these vessels that give the appearance of well defined rounded lobules separated one from the other by connective tissue, since they tend to course along the "continental divides." It is an artefact pure and simple produced by the necessity of making thin cross sections for minute study. What is seen are cross sections of branches of the larger real acinus or lobule, which may or may not contain a branch of the central vein. These cross section lobules are not isolated anatomically one from the other, and still less so physiologically.

Physiologically, the passage across the "continental divide" from one lobule to the other is not marked by any boundary whatever. That which is often seen and usually interpreted as the boundary between lobules is really a "tunnel" or path within which the portal vein and hepatic artery traverse the lobule. Such paths are, however, sometimes really located between lobules because it is a vantage point for the distribution of blood or cellection of bile.

In order to have a simple comparison so that the structure of the liver, as a whole, may clearly be visualized in a brief description, it may be regarded as consisting of a vascular skeleton, for the first half of which the lower half of a pine tree is used to represent the hepatic vein and its branches, the pine needles representing the ultimate or so-called central veins of the lobules. If the parenchyma of the liver can be imagined to have been poured into the lower half of the tree, like batter into a mold, filling out all spaces in the interstices between the branches, the best concept of the gross, and at the same time histologic, relationship of the parenchyma to the hepatic vein would be obtained. If one could imagine this artificial, half-finished liver to have been completed by introducing at some point on the upper surface another lower half pine tree so inserted into the original mass that its branches fit and dove-tail between the branches of the original tree, the second representing the portal vein, a reasonably understandable concept of the relations of the hepatic vein, parenchyma and portal vein will be gained. It would, at the same time, permit one to accept the usual concept of the liver lobule or acinus and at the same time shatter it by showing that no lobule is entirely independent and separate from its neighbor. If one could still further imagine these two trees fitted one into the other so accurately that not only the branches would fit between each other, but the needles on the branches of one fit between the needles on the branches of the other, one would have a conception of the intimate relationship of the ultimate branches of portal and hepatic veins.

In order to understand the relationship which the hepatic artery and biliary ducts bear to the whole, one needs to return to the moment when the second half tree was introduced into the half finished liver and imagine a dense net-work of vessels having been wound about the branches of the second half tree, one red to represent the hepatic artery, the other green to represent the biliary ducts.

Obviously a description of this sort is purely artificial and does not consider the embryologic facts, yet it is far more nearly correct than the description given in courses on histologic anatomy, which also clearly ignore the embryology. In fact, most slides for histologic study are derived from the liver of the pig, because it is peculiarly rich in

connective tissue. This makes the so-called lobule or acinus appear especially distinct, particularly for teaching purposes, and erroneous teachings at that.

The plan of building up an acinus about a single unbranched, central (efferent) vein in this manner and using it as an index of a typical lobule, surrounding it with columns of liver cells and then completing the lobule as it were, by pasting the afferent portal vein and hepatic artery on the finished lobule without showing its relationship to its neighbors is irrational and leads to false notions of simplicity. It would seem far better were we taught from the very outset how complicated the structure and relationship of the lobule really are. And yet the behavior of the liver in certain circulatory disturbances, particularly high grades of passive congestion, make it appear that these artificial structures or lobules functionate or behave more or less as structures of some independence.

Mall injected livers through the hepatic vein and after corrosion demonstrated that it branches very freely, that there is no such structure as a separate terminal central vein for each lobule, but rather that the peripheral or terminal branches anastomose freely. Reconstruction of the lobules about these veins produces an exceedingly complicated outline, not at all rounded or polyhedral as is usually taught. Such areas susceptible of apparent demonstration in slides are artefacts, as previously stated, produced by making cross sections of small branches of the lobule. The real lobule is a considerable mass of liver tissue enveloping a radical of the hepatic vein and its branches, penetrated and "tunnelled" by Glisson's capsule with contained vessels and ducts, so that afferent blood is introduced into it at many points. Such a lobule, if torn from its site, would be shaped roughly like an irregular pine tree, or, better still, a misshapen pine tree. It may have some branches or processes extending far afield, it may be bent on itself, or show marked twists or bends. Most important of all it would not "shell out" of a connective tissue capsule, because it has none. Its margins or outer surface would be ragged for there is no sharp demarcation between lobules, therefore, it would be torn from its surroundings. Moreover, its communications with neighboring lobules would be shown by the mouths of gaping veins which had, when in situ, communicated or inosculated with those of nearby lobules. The "water-sheds" between areas of the same lobule tributory to one or another branch of its central vein are imperceptible and unmarked, indeed they may shift depending on secretory and circulatory exigencies. Exactly the same may be said of the greater "continental divides" between distinct lobules.

While this, in its essence, is not fundamentally different from the usual idea, it is of value when the finer pathologic anatomy of the

liver is under consideration, especially when an attempt is made to explain the long strands of passive congestion in the cyanotic liver or the long connective tissue strands of cirrhose cardiaque.

PATHOLOGY

The cirrhotic liver as it is seen at the necropsy presents certain changes, usually a diminution, occasionally an increase, in size, hobnail surface, and increased consistency and stiffness.

Examining the cut surface, three types of tissue, in varying relative quantities are found: (a) normal liver tissue; (b) nodules of liver tissue, lighter in color, varying in size from that of a millet seed to that of a large bean or occasionally a walnut, and (c) connective tissue.

The entire surface has a tawny to brown color, varying with age and degree, which led Laennec to give it the name cirrhosis. This color is produced by a histologic finding of considerable importance to be described later. No particular naked eye changes can be noted in the smaller blood vessels, except that the small dark area in the center of the acinus is entirely absent in the nodules, that is to say, the usual index of the acinus, the central vein, is absent.

Closer study of these nodules shows that they vary in size, are of paler color than normal liver tissue, and that they are likely, on cut section, to be elevated slightly above the level of surrounding structures, be it normal liver or connective tissue. They are not always rounded or oval but may at times show several rounded eminences as though a cluster had been cross sectioned. Examination of these nodules for the position of the efferent lobular (central) vein shows a very wide variation from the normal. It is no longer central but eccentric, often peripheral and occasionally actually beside the nodule, gathering its blood from the body of the nodule by exceedingly fine capillaries, whose walls correspond to Kupfer's cells. This can have but one meaning, namely, asymmetric destructive processes and, as a corollary, asymmetric regenerative processes. The nodules of lighter colored liver tissue, now universally accepted as regenerated liver cells, show a total absence of the acinal markings. The smooth continuity of liver tissue has disappeared; the nodules are isolated one from the other by strands of connective tissue, although clusters are sometimes seen. These clusters are usually regarded as being produced by budding from a parent mass rather than by a confluence of several groups or masses. Sometimes the nodules take up most of the cut surface; at other times almost the whole organ is composed of connective tissue with very small occasional nodules of liver tissue, often stained a deep green (bile stasis).

Further study of the blood vessels in any cross section shows that the larger vessels are closer together than normal. This corresponds to the general reduction in the mass of the liver.

The color of the cut surface is variable depending on the age of the patient as well as of the disease. The older both are, the darker the brown color. If there is much fatty degeneration or infiltration, there is a distinct yellow color, especially is this true of the nodules. Extensive hemosiderosis is the cause of the rusty or tawny color that gave the disease its name. Occasionally in the presence of jaundice, the liver is green in color.

The connective tissue is tough, present in varying quantities, depending on the degree of the disease, and in color varying with that of the liver in general. Where the connective tissue has shrunken considerably, it may be very white and shiny, but when so shrunken it is particularly likely to be associated with jaundice and to be dark green. The capsule, in general, follows the connective tissue in appearance.

The areas of normal liver tissue, if any remain, differ very little from the tissue of a healthy liver. It shows the same brownish liver color, with soft texture, and if there be sufficient passive congestion, which is nearly always true, the acinus markings are clearly visible.

If attention be directed to the histologic picture, one finds an extremely varied type of cell as well as a very unfamiliar general structure. The liver cells may show the following variations (though not all in any given slide): (a) Normal cells in the familiar radial arrangement; (b) normally arranged cells in various stages of retrogressive changes chiefly fatty degeneration, also parenchymatous degeneration and possibly actual necroses. These are original liver cells in process of destruction; (c) among the above normally arranged cells may be found large, very pale cells with unusually clear protoplasm, occurring singly or in groups, sometimes among the degenerating cells, sometimes wholly surrounded by connective tissue. Since there is no evidence of circulatory obstruction such as engorgment of capillaries, these cells could not have been snared off by contracting strands of connective tissue. Their clear, pale protoplasm with larger cell bodies at once proclaims them as newly formed cells, regenerated cells, if you please; (d) very large groups of the same type of cell, arranged more or less in parallel columns but entirely without radial arrangement or central vein, with an eccentrically placed vein. These represent nodules of regenerated cells with a new type of vascularization; (e) greatly increased numbers of bile ducts in the connective tissue surrounding the nodules; (f) among the cells of (c) and (d) may be found cells in various stages of degeneration.

It was with a definite purpose in mind that I described the normal liver structure in terms of its circulatory elements. I will consider more carefully the circulation of the cirrhotic liver.

During injection experiments on cirrhotic livers carried out by Kretz,[24] or under his direction, the following observations were made. If the injection mass was introduced through the portal vein it would appear in the hepatic vein at a time when large areas of hepatic tissue were still uninjected. These uninjected areas proved to be the larger nodules of newly formed liver cells as well as the small groups of isolated liver cells previously mentioned. If the hepatic artery was injected by a celloidin mass of different color it would be discovered that it was exactly these areas that would be injected. It was also noted that the hepatic artery was hypertrophic in such cases.

But one conclusion can be drawn from these findings, the regenerative process is directly under the nutritional influence of the hypertrophic hepatic artery. The portal vein continues to supply the original liver tissue, which has escaped the destructive influences of the disease and possibly some of the newly formed or regenerated masses of cells slightly or indifferently. Since the new groups of cells are drained chiefly by newly formed eccentric "central veins," a new communication between the hepatic artery and the portal vein is established via branches of the hepatic vein. Under the normal circulatory relationship between hepatic artery and portal vein, the latter is not embarrassed by the greater pressure of the hepatic artery, but with the opening of new channels through the regenerated nodules the anastomosis is much more extensive and free. This, plus the hypertrophy of the hepatic artery, leads to definite embarrassment of the portal circulation. It is like making an anastomosis much greater in size than the usual capillary transition between an artery and a vein, at the same time that the artery in question has had an opportunity to hypertrophy. Venous stasis and edema must result. This is probably the real reason for portal stasis and ascites, certainly when they appear before connective tissue production has taken place in the liver. The fact that injections of the portal vein in cirrhotic livers fail to fill large areas of liver tissue, newly formed to be sure, but liver tissue nevertheless, demonstrates the presence of an internal collateral circulation that is never mentioned when the collaterals of cirrhosis of the liver are described.

It has been shown by Ponfick that large masses of liver tissue may be resected in dogs only to have a regeneration take place adequate for the physiologic needs of the animal, plus a large margin of safety. The question arises whether this internal collateral circulation or anastomosis of the portal vein around rather than through the newly formed nodules in cirrhosis of the liver, is not the leak which is responsible for the hepatic insufficiency in this disease. To put it another way, is it not because the portal blood is carried past the nodules of regenerated liver cells rather than through them that insuf-

24. Kretz: Verhandl. d. deutsch. path. Gesell. 8.

ficiency results? The liver is doubly insufficient, first by reason of its parenchymatous loss, but also because the portal blood fails to reach the parenchyma in adequate quantities by reason of both internal and external collateral circulation. In spite of the parenchyma loss had the circulation been rebuilt properly, relative hepatic sufficiency would have prevailed much longer than is usually the case.

HISTOPATHOLOGY

Liver.—The microscopic picture is essentially one of disorder and disarrangement. In a well marked case there will be seen extensive areas of connective tissue arranged in strands or streets irregularly disposed, crossing and recrossing each other. In the meshes will be seen masses of liver cells in most unusual and disorderly arrangements. The cells are disposed more or less in parallel columns, but there is no evidence of systematic, much less systematic radial, arrangement. Efferent veins will not be found in these masses, or, if so, they will be eccentrically placed or in still other cases be found beside the cells. The portal vein will not present the normal close approach, but will be distant in the connective tissue strands in which it probably passes to the side of the nodules, rather than to or through them. The hepatic artery is seen in the connective tissue strands in a loose relationship to the portal vein. That it supplies the nodules with their afferent blood, as maintained in Kretz, cannot be demonstrated histologically. It is an assumption based entirely on his injection experiments. The capillaries in the nodules lying as they must between the columns of cells, have become intricate networks or labyrinths from which the efferent blood has great difficulty in escaping.

Occasionally, quite normally arranged liver lobules, with radiating cell columns—central veins and portal vein in normal contact—may be found, residuums of the original liver structure. Degeneration or necrosis, if seen at all, is most likely to be found in these lobules, though lesser retrogressive changes, especially fatty degeneration, are often seen in the cells of the regenerated nodules.

In the connective tissue strands are seen inumerable freely branching ducts, lined with cuboidal cells with deeply staining nuclei. These are newly formed bile ducts. They probably possess a double function. They are making unusual efforts by proliferation and branching to search out and assume contact with the new nodules for purposes of bile drainage, and, in addition they are probably concerned in the formation, in small part at least, of new liver cells, for they are genetically closely related to them. MacCullum has demonstrated this transformation several times in histologic slides by showing their transition and union with the liver cells in nodules or groups of newly formed cells.

The connective tissue strands are irregular in size and vascularity. The variations in size are dependent on the amount of destroyed liver tissue represented, that is to say, a large thick strand represents the collapsed skeleton of a large area of destroyed liver, a small strand less. While the increase in the bile ducts is, in part, absolute, some of the increase is relative, the collapse bringing original ducts closer together. The same is true of the increase in blood vessels—some are newly formed, others have collapsed with the skeleton into closer proximity. Often one can see indications of the lobules (their number, size, etc.) that have been destroyed in an area of connective tissue; it is almost as though the parenchyma had dropped out and the skeleton collapsed. The connective tissue is increased relatively as well as absolutely. Many round cells and wandering cells of all types are found in these areas.

Hemosiderin deposits in cirrhotic livers are extremely frequent; when diligently searched for, are found in more than half the cases. In studying old slides in our possession, derived from cases of cirrhoses of varying degrees, it was present in all of the more advanced cases. It is true that in some cases special stains may be necessary, yet when searching carefully, minute deposits will be found either in the connective tissue or the liver cells themselves. It is because it is not so overwhelmingly present as to be immediately striking that this finding is not more often described. Just why this should be found in a degenerative disease of a parenchymatous organ has been the subject of much controversy. It was to be expected during the early days of the literature of cirrhosis that it would be associated with and regarded as dependent on hemorrhages in the gastro-intestinal tract, absorption being through the portal system with subsequent deposit in the liver. Kretz [25] was the first to set up the hypothesis that this pigment was liberated by destruction of red blood corpuscles in the liver, probably by the action of a circulatory toxin, possibly a known chemical such as alcohol. Bleichroeder [26] has written very extensively on this phase of the pathology of cirrhosis.

To forestall any misapprehension we are not, when making these statements, thinking of cases of so-called bronze diabetes but of portal cirrhosis.

Spleen.—The spleen is very much enlarged, often it is much larger than the liver. There has been much controversy over the cause of this enlargement. Most of us were taught, and it is still believed by some, that this enlargement is due to the passive congestion associated with cirrhosis of the liver. There is, however, much accumulated evidence that there is a distinct pathologic process in the spleen typical

25. Kretz: Beitr. z. klin. Med. u. Therap., 1896.
26. Bleichroeder: Virchows Arch. f. path. Anat. **177.**

of cirrhosis of the liver. There are, for example, many cases of cirrhosis in which the spleen is greatly enlarged long before there is ascites, that it to say, long before passive congestion has occurred. Leichtenstern [27] was the first to call attention to these cases, indeed, he regarded them as pre-cirrhotic and called them by the name "Pre-cirrhotic Splenic Tumor." However, he is scarcely justified in the conclusion implied by the name, that the spleen is diseased before the liver, for cirrhosis is an insidious disease, it is always quite advanced before a diagnosis is made; in fact, the clinical manifestations of its early stages are entirely unknown. The splenic enlargement is always considerable, it is much greater than that of cardiac decompensation. It is not nearly as hard, either to palpation of the intact organ or when its cut surface is examined. The spleen of passive congestion gives the impression of being stuffed full to bursting, yet on the cut surface the pulp does not pout, nor can it be scraped off, both evidences of great increase in connective tissue. The spleen of cirrhosis is slightly softer, more like that of a subacute infection, its pulp usually pouts on the cut surface and can be scraped off readily. Its color is lighter than either the normal or the cardiac spleen, often having a slightly grayish tinge as though milky water had been poured over it, or it may have a rusty, tawny tinge. Bleichroeder found a considerable difference in the specific gravity, the spleen of cirrhosis on an average having a specific gravity of 1.059 against 1.044 for passive congestion.

Histologically, the spleen of cirrhosis shows a slight congestion as compared with the normal; presumably this is passive, but it does not approach that of the spleen of chronic cardiac decompensation. Furthermore, there is a great increase in the various types of wandering cells and lymphocytes. Various writers have described circumvascular proliferations which at times penetrate the blood vessels, one of them (Bleichroeder [28]), attributes to these a special pathogenetic significance, believing that they may become dislocated and swept from the spleen to the liver, there producing either focal necroses or setting up the inflammatory process that eventuates in the destruction of normal liver tissue.

Finally, there is a great deposit of hemosiderin and various other iron pigments, chiefly in the connective tissue of the spleen but also in the pulp and in the various wandering cells. The source of this is not yet clearly understood, but the assumption that it arises from extensive destruction of red blood corpuscles is as justifiable here as it is for the origin of the same deposits in the liver. Often it gives the spleen a slightly rusty or tawny color.

---

27. Leichtenstern, quoted by Naunyn: Verhandl. d. Deutsch. path. Gesell. 8.

ASSOCIATED PATHOLOGY

Embarrassment of the portal circulation leads to various disturbances. First among these is ascites. This is often of extreme degree.

Passive congestion leads to a catarrhal pseudo-inflammation of the gastro-intestinal mucosa. The mucosa of the stomach is intensely injected, edematous and at times shows submucous extravasates. In well marked cases these may be very great and lead to distressing hematemesis. The mucosa is covered by an exceedingly tenacious mucus, often containing exfoliated epithelium and red and white blood corpuscles. The mucosa and serosa of the stomach and sometimes of the bowel are often tinged a faint brown by hemosiderin deposits, a finding attributed by some to the results of passive congestion and extravasates, by others to processes identical with those causing similar deposits in the liver and spleen. These are never seen in the stomach in the passive congestion of cardiac decompensation.[28]

Collateral venous hypertrophies or varicosities reach extreme degrees and represent efforts of the portal blood to reach the right heart by routes other than the normal. They are most marked in the anastomosis of the portal circulation with the systemic veins at the lower end of the esophagus and between the portal and systemic veins in the lower rectum via the hemorrhoidal veins and via the veins of the abdomen, the so-called caput medusae. It might be well again to mention the collateral circulation around the nodules of regenerated cells within the liver itself.

Obscure Indefinite Findings.—There is always a very low grade of secondary anemia present, the nature of which is not well understood, whether it is dependent on the same noxious agent that produces cirrhosis itself or on associated digestive and consequent nutritional disturbances is not yet settled. Possibly, it may be regarded as an abortive anemia of one of the types often associated with cirrhosis.

The heart usually shows slight myocardial changes of a degenerative nature. Whether this is dependent on the toxins producing the disease or on the toxins produced by the disease is not clear.

Most cirrhotic patients are slightly jaundiced, not the clear-cut yellow color seen in biliary obstruction, but a pale, almost imperceptible color, which seems to give an undertone of yellow to all light colored surface tissues, particlarly the sclerae and the skin of the covered parts of the body. The color is very much like that of low grade sepsis. The urine contains large amounts of urobilin and urobilinogen. The conclusion that this color is due to urobilin seems justifiable. True jaundice occurs in some cases, especially when contraction of the connective tissue has embarrassed biliary circulation.

28. Wagner: Arch. f. klin. Med. **34.**

Occasionally peculiar hemorrhages or ecchymoses are seen in the conjunctiva, the retina and the skin, especially where the texture is soft. These and the clinically noted attacks of epistaxis are as yet not satisfactorily explained. They remind one of the dyscrasias of certain blood diseases.

There are several notations in the literature of transformation of the normal into red bone marrow, especially in the femur.[29] Bleichroeder [26] maintains that this is true in the majority of cases, he having found changes in the upper end of the femur in twelve or thirteen cases examined for this change.

In certain instances, particularly those in which there is a very large spleen, there are very marked sclerotic changes in the splenic artery and vein and also in the mesenteric veins. Just how this is brought about is not very clear. It is most often present in Banti's syndrome and could be used as a particular argument against Banti's contentions. If the toxin producing cirrhosis originates in the spleen alone, why does it produce sclerotic and hyalin degeneration of identical nature in the mesenteric veins? Just this finding is particularly suggestive of an enteric origin for the poison though of course it does not explain why the splenic artery and vein should be similarly involved.

Tuberculosis, or rather, isolated occasional tubercles in the peritoneum, and the cirrhotic liver itself are frequent, apparently accidental findings. They are usually explained as having developed by virtue of the generally lowered resistance of the patient, and are believed to be terminal or subterminal events. Others see in them a close relationship etiologically. This phase of the subject has been given much study but without definite conclusions. Some writers have made a separate classification of these and called them tuberculous cirrhoses, a step scarcely warranted at present.

RELATION TO OTHER DISEASES

Banti [30] described what he believed to be a syndrome with a definite pathologic complex, worthy of separate classification. He set up certain requirements that make his definition exceedingly complex, indeed it is often regarded as impossible. There must be no known etiology for the disease; there must be enlargement of the spleen preceding the cirrhosis and anemia, which must be of a secondary type with a low leukocyte count, but relatively a lymphocytosis; and the disease must be separable into three stages: (a) splenomegaly; (b) anemia; (c) cirrhosis of the liver with ascites.

Banti himself does not always write in the same vein. More recently [31] he maintains for the disease a characteristic pathology, par-

29. Zypkin: Virchows Arch. f. path. Anat. **174.**
30. Banti: Sperimentale, 1894, p. 407.
31. Folia Haemat. **1**:11, 1910.

ticularly in the spleen. He speaks of it as a "fibroadenie," which is essentially a fibrosis of the malpihgian follicles situated around the splenic artery which itself shows hyalin changes, and an extensive fibrosis of the splenic reticulum. All of this he believes to be of noninflammatory origin, because he has not found fibroblasts present. There is hyalin degeneration of the capsule of the spleen, and cirrhosis of the liver differing in no respect from the usual picture, except in the splenic changes mentioned. Blood-pigments were not found in the spleen or liver in his cases, hence he assumes that there was no blood destruction. The red bone marrow of secondary anemia is uniformly found. He assumes that there is an infectious agent producing the splenic changes ("fibroadenie") which, in turn, cause the spleen to elaborate a poison producing the liver cirrhosis. There is no known analogy for this in all pathogenesis, it is manufactured to fit the case, a reasoning from effect to cause.

Banti admits that the diagnosis cannot be completed until the liver is seen by the pathologist (or surgeon) and that the pathologist cannot make the diagnosis without the clinical data, namely the history of three consecutive stages, splenomegaly, anemia and cirrhosis. This is merely another way of saying that the disease is essentially undiagnósticable.

In a general way, the literature may be divided into two classes with reference to the acceptance or rejection of Banti's disease as a clinical entity: (1) That of authors who accept it, usually clinicians, with the notable exception of Naunyn,[27] and (2) that of authors who reject it, generally speaking, pathologists, though they usually manifest a more scientific conservatism and may be said to assume an attitude of skepticism.

While I have never seen a case classifiable as Banti's disease, it seems to me that there is no definite reason why it should at present be accepted as a clinical entity. There is too much controversy concerning it, and Banti is neither definite nor sure enough of himself. Finally, if we accept Banti's classification, there is no such disease as splenic anemia, for he does not permit even this to escape him, maintaining that it is Banti's disease in the second stage before cirrhosis has had time to develop.

Banti's contention that a poison is developed in the spleen has been supported in a scientific manner but once, and never since confirmed. Umber [32] made metabolic studies on a case and found that there was disintegration of the blood albumins on a toxemic basis. After extirpation of the spleen this ceased. This is possibly analogous to some of the experiments of Longcope, interpreted by him as anaphylactic phenomena. This is not to be construed as an effort to state that toxins

32. Umber: Ztschr. f. klin. Med. **55**: 1905.

cannot originate in the spleen, it has not been proved in cirrhosis. On the other hand, it seems proved in both splenic anemia and in hemolytic jaundice by the results obtained by splenectomy.

Mayo [33] arguing on purely clinical grounds, experience, if you please, states that extirpation of the spleen in cirrhosis, when the spleen is very large, is beneficial by reducing the volume of portal blood so that the liver may again "carry on." He suggests, however, that it may prevent "those irritants" ordinarily filtered out in the spleen from reaching the liver as, for example, in splenic anemia. He offers no proof of their existence. Again the alluring theory, that abnormal splenic metabolic products are the cause, cannot be resisted by one usually so matter of fact that theories have no place in his articles.

Every patient with cirrhosis of the liver is anemic or shows periods of anemia, of the secondary type. Every case shows great variations in its course, not only as to symptomatology but as to duration of the disease. It would seem more rational then to regard Banti's syndrome as one of the various clinical pictures under which cirrhosis may present itself. Moschcowitz [34] assumes this attitude with great emphasis, probably because the two cases presented in his article showing Banti's syndrome clinically, failed to show any evidences whatsoever of cirrhosis at necropsy.

It strikes me that Banti has surrounded his definition with so many conditions and modifications, some reasonable and some—e. g. his contention that the etiology must be unknown—so unreasonable as to make the disease purely imaginary. Dropping it will still leave a diagnostic pigeon-hole for all cases. Chronic cirrhosis with high grade anemia and splenomegaly will describe Banti's typical cases. Splenic anemia will cover those cases claimed by him to be in the second stage before cirrhosis has had time to develop.

Diabète Bronzé.—Diabète bronzé, or cirrhosis pigmentaire, is a disease of obscure origin characterized by a cirrhosis of the liver like that of portal cirrhosis with extensive visceral and cutaneous hemosiderosis, and diabetes mellitus.

Various theories of its pathogenesis are offered, the chief of which, ascribe the primary rôle variously to the hepatic cirrhosis, to the diabetes and to the hemosiderosis. Another somewhat differing etiology is offered in the form of an hypothetical toxin the cause of all the other pathologic changes. Under this characterization it is spoken of as hemochromatosis.

It is an extremely rare disease, the literature offering only seventy-five cases for study. In a general way they may be divided into two

33. Mayo: Ann. Surg. **68**:183 (Aug.) 1918.
34. Moschcowitz: J. A. M. A. **69**:1045 (Sept. 29) 1917.

groups, one, those in which the cirrhosis and pigmentation represent the less severe form, the other—probably an advanced stage—in which diabetes mellitus has been added to the foregoing changes.

The pathology of the cirrhosis differs but little from that of ordinary portal cirrhosis; the liver is usually larger than normal, death occurring before atrophy can occur. Ascites is rare. There are no distinctive features in the associated diabetes; it develops in the great majority of cases and is the cause of most of the deaths. It may be due to extensive hemosiderotic fibrosis of the pancreas.

Usually a moderate degree of secondary anemia is present.

Wilson's Disease.—The association of cirrhosis of the liver with a definite disease of the nervous system described by Wilson in 1912 is a most remarkable combination, an incongruity pathologically. It is a progressive degenerative disease located in the lenticular nuclei occurring in young adults, familial in occurrence, yet not hereditary. Its chief manifestations are various motor phenomena of extra pyramidal origin with some mental symptoms. Atrophic cirrhosis of the liver is constantly found. Aside from its remarkable association with a nervous disease, it is noteworthy that it occurs in youth, is familial, that alcohol is not implicated in its etiology, that ascites and other evidences of portal stasis are absent, and that clinically the cirrhosis is not demonstrable, even the small size of the liver has only rarely been demonstrated clinically. Wilson characterizes the changes in the liver as a multilobular or mixed cirrhosis.

CLASSIFICATIONS OF CIRRHOSIS

So very much has been written in efforts to prove that all cirrhoses are essentially the same process that we will venture a few remarks on this subject.

Mayo [32] is the most arbitrary of all writers and brusquely divides them into portal and biliary cirrhoses. The former is what is generally known as Laennec's cirrhosis, but he also includes all forms of hypertrophic cirrhoses, whether of alcoholic or other origin. He does not accept the view that the enlarged livers of certain types of cirrhosis, often containing considerable fat, later become atrophic. He therefore speaks of atrophic portal cirrhosis which he regards as the characteristic response to concentrated spirits, such as gin, and to pepper excess, and to poisons carried to the liver from the spleen. On the other hand, he speaks of hypertrophic portal cirrhosis which is the characteristic response to excesses of beer, and is associated with fat deposits. Biliary cirrhosis is dependent on infection of the biliary ducts, and is characterized by a large liver and a very large spleen. Mayo's classification could be summarized thus: (*a*) Portal cirrhosis, (a) atrophic type (Laennec); (b) hypertrophic type, (*b*) biliary cirrhosis, with an enlarged liver.

In his opinion, there is no pathologic or clinical basis for a separate classification of Hanot's cirrhosis. He believes that the disease so designated is either an obstructive biliary cirrhosis or an hemolytic icterus, in which there is work hypertrophy of the liver. Since hemolytic icterus is very frequently associated with gallbladder pathology (more than 60 per cent. of the cases), he believes that there are combinations of the two, that is to say, a work hypertrophy due to hemolytic jaundice plus biliary cirrhosis of infectious origin.

Pathologists still adhere to a much more elaborate scheme: (1) Laennec's cirrhosis (atrophic), including multilobular cirrhosis, nature not clear, probably syphilitic. (2) Hanot's cirrhosis (primary biliary hypertrophic cirrhosis). (3) Obstructive biliary cirrhosis. (4) Hepar lobatum. (5) Cirrhose cardiaque.

A brief description of the nonportal cirrhoses and other diseases sometimes confused with Laennec's type of cirrhosis will serve to clarify some of the difficulties in classifying them.

Hanot's Cirrhosis.—In 1876 Hanot presented for clinical and pathologic study a type of disease, la cirrhose hypertrophique avec icteré chronique. He based his studies on four cases of his own and about a dozen cases collected from the literature. The disease is characterized by a chronic intermittently fiebrile course, with severe jaundice but without clay-colored stools or ascites, with a very large, smooth liver and a very large spleen. Histologically, there is a striking intraacinous development of connective tissue. In later publications he broadens his views considerably, so that it becomes somewhat difficult to know just what he includes. Still later writings are even less clear, and his original ideal type becomes confused. Perhaps he was led afield by other French writers who described various "forms" of Hanot's cirrhosis, some accepting as a standard the presence of intraacinous development of connective tissue, others described a capillary cholangitis as the essential pathologic standard. As will be seen later, they were doubtless describing what is now called obstructive biliary cirrhosis. In answering these writers in the course of a long series of polemical articles, he allowed himself to become confused until his articles lost much of their clearness, and, like Banti, he did not seem to know just what constituted a clear-cut type, an ideal of the disease known by his name.

Today a somewhat broadened or modified view is taken as to what constitutes Hanot's cirrhosis. There are two distinct types or forms: *First*, those cases of cirrhosis in which there is a degenerative process in the liver associated with a toxemic jaundice. This description is strikingly like that of Mayo, who uses it to deny Hanot's cirrhosis a separate place in pathology, but terms it hemolytic jaundice with

work hypertrophy. However, these cases are said by Kretz [35] to develop an ascites if they live long enough, because of changes in the texture of the liver with contraction or atrophy, therefore, they do not conform to Hanot's requirements of an absent ascites, and are not his ideal type. These show no inflammation of the finer bile ducts but there is a very fine intralobular almost intercellular distribution of connective tissue breaking up the lobules into very small groups of cells. *Second,* those cases of jaundiced hypertrophic cirrhosis in which there is an intense capillary cholangitis, a type brought forward by Heineke [36] as the ideal type of Hanot. The connective tissue about the biliary capillaries proliferates and secondarily enters the acini insinuating itself between the cells. It shows no tendency to contract and cause atrophy of the liver, the feature which differentiates it from obstructive biliary cirrhosis. Its etiology is clearly infectious. In both types the liver is large, hard and smooth, often weighing as much as 5,000 gm. The spleen is also large and hard, much greater in size than in atrophic cirrhosis. Doubtless many cases of Laennec's cirrhosis with enlarged liver are erroneously described as being of Hanot's type.

Obstructive Biliary Cirrhosis.—Obstructive biliary cirrhosis is an exceedingly rare type. The liver is small, very hard, like leather, and is very dark green in color because of its etiology, chronic obstructive jaundice. Probably, one reason this disease is so rare is because modern surgery does not permit an obstructive jaundice to exist long enough to produce the consequent changes unless it be due to an exceedingly slowly progressing carcinoma of the gallbladder. Histologically, there is still normal acinal structure with intense bile stasis and consequent destruction of liver cells. These are destroyed in part by the biliary stasis and back pressure, but, perhaps, still more by the consequent chronic infection which is always associated, either sooner or later. A thick connective tissue mantle is formed about the biliary ducts and capillaries, associated with the histologic phenomena of inflammation.

Hepar Lobatum.—While often classified with the cirrhoses, hepar lobatum does not properly belong here. It is essentially normal liver tissue traversed by long, deep scars communicating with each other and dividing the liver into adventitious lobes. They are the remains of gummatous processes, and are often characteristically localized in the left lobe of the liver. Sometimes it is a mere connective tissue or scar-like membrane.

Multilobular Cirrhosis.—Multilobular cirrhosis is not clearly classified. The term is reserved by some writers for the end-result of gummatous hepatitis in children. The liver is small, roughly resem-

35. Kretz: Verhandl. d. Deutsch. path. Gesell **9.**
36. Heineke: Beitr. z. path. Anat. u. z. allg. Path. **22.**

bling that of Laennec's cirrhosis but not quite so tough. There are relatively large pseudo-acini produced by connective tissue subdivision of normal liver tissue in which true acini are present. Histologically, the connective tissue strands are broad, but differ from those of Laennec's cirrhosis in that there are no evidences of inflammatory infiltration, it is clearly a quiescent scar tissue. Biliary ducts show no evidences of sprouting and there is little or no parenchymatous regeneration. Normal acini clearly differentiate it from atrophic cirrhosis.

Cirrhose Cardiaque.—Cirrhose cardiaque is not a cirrhosis at all; it is a high degree of passive congestion in which the parenchymatous cells destroyed by back pressure of the blood have been replaced by connective tissue. It has been credited with a specific infectious etiology because it is most typically found in cases in which the cardiac difficulty was acquired in early youth especially in concretio pericardii cum corde.

RÉSUMÉ OF CLASSIFICATION

The following would represent a comparison of the orthodox classification of pathologists with the abrupt of Mayo, indicating the equivalents.

Pathologists' Classification	Mayo's Classification
1. Laennec's cirrhosis.....	
2. Biliary cirrhosis	2. Hemolytic jaundice, with work
(a) Primary biliary Hanot	1. Portal cirrhosis.
I. Toxemic without biliary capillary infection	hypertrophy.
II. Biliary capillary cholangitis	3. Biliary Cirrhosis.
(b) Biliary obstructive....	3. Biliary Cirrhosis.

3. Multilobular cirrhosis, probably an end-result of syphilis in childhood.

4. Hepar lobatum—post syphilitic scars.

5. Cirrhose cardiaque.

In closing, I cannot resist the temptation to give expression to a thought, which is growing into a conviction, that when dealing with cirrhosis of the liver we must regard it as closely allied to the diseases of the blood, for the following reasons. Banti's disease is an accepted blood disease, associated with cirrhosis of the portal type. Splenic anemia if accepted as a clinical entity always suggests liver changes to the clinician, a suggestion born of an involuntary association of the two, based possibly on Banti's writings. Diabété bronzé is a typical

cirrhosis and diabetes plus a marked disturbance in the metabolism of iron and a moderate anemia. From this to the hemosiderosis of ordinary atrophic cirrhosis is not so far a cry as to be unheard, especially if the latter be associated with an anemia. The jaundice present in most cases of cirrhosis is urobilin jaundice, probably the same substance which causes the yellow color in pernicious anemia. Some writers who have made special search have found red bone marrow of the type seen in the high grades of anemias. While it is true that this has not been found by many clinicians, it is also equally true that very few have searched for it. Finally, when we begin studying hypertrophic cirrhosis we find such practical men as Mayo abandoning the term hypertrophic cirrhosis and visualizing it as a work hypertrophy in hemolytic jaundice, a disease which is unquestionably classifiable as a disease of the blood.

THE ANTIDIURETIC EFFECT OF PITUITARY EXTRACT APPLIED INTRANASALLY IN A CASE OF DIABETES INSIPIDUS *

HERRMANN L. BLUMGART, M.D.
BOSTON

INTRODUCTION

The combination in diabetes insipidus of insatiable thirst and polyuria interfering with sleep and all the ordinary activities of life naturally has stimulated numerous workers in the past ten years to devise some method whereby the lives of the sufferers of this disease could be made more tolerable. In 1913, Von der Velden [1] and Farini [2] demonstrated that the subcutaneous injection of pituitary extract checked both the polyuria and the polydipsia. This observation has been abundantly confirmed. Two features of hypophyseal therapy render it still highly unsatisfactory. First, the effect is transitory, and, second, hypodermic injection has always been essential and is inconvenient and difficult for continued use of patients.

Even though the effect is transitory, however, if pituitary extract could be introduced into the body in more frequent doses and in a less inconvenient manner, great comfort would naturally result. Absorption by way of the gastro-intestinal tract has been tried by many observers. Failure has attended practically all attempts to diminish the urinary output by dried extract given by mouth. Motzfeld [3] controlled the diuresis in one case by feeding fresh posterior lobe of the ox. Christie and Stewart [4] were, however, unable to confirm this result in their case. Christian,[5] in a case studied by him, found that pituitary extract introduced in suppositories, by colonic irrigation, and in gumdrops which were allowed to dissolve slowly in the mouth, failed to exercise any antidiuretic effect.

In the case under observation only 0.005 c.c. of pituitrin "O" [6] subcutaneously was necessary to effect a marked diminution in the

---

* From the Medical Clinic of the Peter Bent Brigham Hospital

1. Von der Velden, R.: Berl. klin. Wchnschr. **50**:2083, 1913.
2. Farini, A., and Ceccaroni, B.: Gazz. d. osp., Milano, **34**:879, 1913; Clin. med. ital., Milano **52**:497, 1913.
3. Motzfeld: Endocrinology **2**:112, 1918.
4. Christie and Stewart: Arch. Int. Med. **20**:10 (July) 1917.
5. Christian: Med. Clin. N. America **3**:849 (Jan.) 1920.
6. Pituitrin "O" is the aqueous extract of the posterior lobe of the pituitary prepared by Parke, Davis & Company for obstetric use and is one-half the strength of pituitrin "S" prepared for surgical use.

urinary output. Since so small an amount was effective and since certain methods had not been attempted, it seemed worth while to undertake the following study.

REPORT OF CASE

G. C., (No. 31,569), a schoolboy, aged 16, entered the Peter Bent Brigham Hospital Nov. 28, 1921, complaining of thirst and frequency of urination.

Family History.—Father, mother, two brothers and five sisters are living and well.

Past History.—Negative, save for diphtheria at 3.

Present Illness.—Patient felt perfectly well until three months before admission when he noted the rather sudden onset of polydipsia and polyuria which gradually increased.

Physical Examination.—Patient was a poorly developed and poorly nourished boy, with slight diffuse brownish pigmentation of the skin over the entire body. Ophthalmoscopic examination was negative. A complete general and neurologic examination, including perimetry, showed no other abnormalities.

Clinical Pathology.—Blood: Hemoglobin was 85 per cent. (Sahli); red blood cells, 4,832,000; white blood cells, 11,300. A stained smear showed definite achromia and slight anisocytosis. The blood Wassermann reaction on two occasions was strongly positive. Blood sugar: 7.1 mg. per hundred c.c. Blood urea nitrogen, 10 mg. per hundred c.c.

The blood Wassermann reaction of the patient's father was very weakly positive.

Urine: Clear, pale, acid, without sediment; specific gravity, from 1.000 to 1.003; no albumin or sugar. Daily urine output varied from 6 to 9 liters.

Spinal Fluid: Clear and colorless; pressure, 155 mm. water; contained six cells per c. mm. Globulin reaction was slightly positive. The Wassermann reaction was weakly positive in 2 c.c. and in 1 c.c.

Roentgen-Ray Examination: Stereoscopic plates of the skull showed no evidence of any abnormality.

METHOD

The procedure employed was as follows: The patient was given a diet containing a fixed amount of protein and salt. This precaution was taken because it has been shown conclusively that the chlorid and nitrogen intake influences the urinary output.[7] Between meals the patient was encouraged to take as much liquid as he desired. He was not allowed to eat between meals nor was he allowed lemonade, coffee or other beverages which might introduce confusing factors. The water content of the food, while not accurately determined, was kept approximately uniform. Under this regimen, the patient's fluid intake was 5,000 c.c. from 7 a. m. to 7 p. m. and about 3,000 c.c. during the night. In order to establish a standard curve of excretion, the 5,000 c.c. intake was distributed evenly throughout the day, 200 c.c. being given every half hour from 7 a. m. to 7 p. m. During the same period, the urine was collected every hour. Under these conditions the fluid intake and output were relatively uniform. Single doses of pituitary extract subcutaneously, intranasally, by rectum and by mouth, and of histamin

7. Oehme and Oehme: Deutsch. Arch. f. klin Med. **127**:261; 1914.

subcutaneously and intranasally were administered. The intake being constant, the effect sought was a delayed excretion rather than a diminution in the total urinary output. This procedure, in excluding subjective factors and ensuring a more uniform rate of excretion makes effects of lesser magnitude discernible.

The methods which gave any indication of influencing the urinary output were then tested by placing the patient on unlimited fluids and noting the effect over twenty-four hours.

OBSERVATIONS

Effect of Pituitary Extract and Histamin.—The patient was put on a fixed intake of 200 c.c. every half hour with instructions to void every hour. On this regimen it was found that no antidiuretic effect was

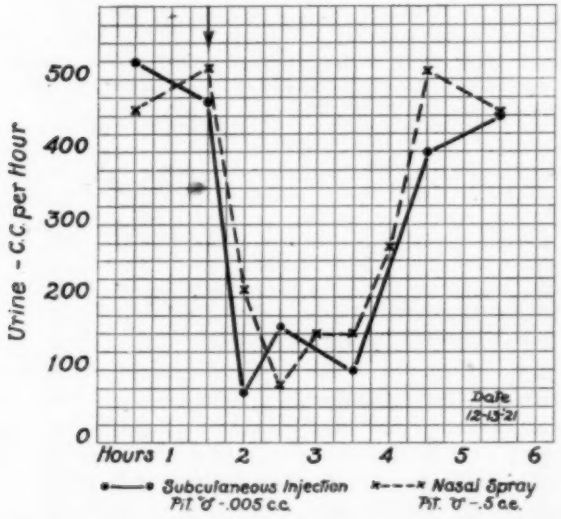


Chart 1.—The comparative antidiuretic effect of subcutaneous injection of pituitrin "O" and intranasal spray of pituitrin "O" with fluid intake of 200 c.c. every half hour. Solid line represents the effect of subcutaneous injection of 0.005 c.c. of pituitrin "O," dashes indicate the effect of 0.5 c.c. pituitrin "O" sprayed intranasally at time noted by arrow.

produced by: (1) 2 c.c. pituitrin "O" retained in the mouth for ten minutes and then swallowed; (2) from 4 to 8 c.c. pituitrin "O" with 20 c.c. tap water introduced by rectum; (3) histamin, 1 c.c. of 1:10,000 solution injected subcutaneously; (4) histamin, 0.1 c.c. sprayed intranasally; (5) tap water 1 c.c. sprayed intranasally. On the other hand, a marked antidiuretic effect was produced by: (1) from 0.005 c.c. to 0.5 c.c. pituitrin "O" injected subcutaneously; (2) from 0.5 to 5 c.c. pituitrin "O" sprayed intranasally (Chart 1; Table 1).

TABLE 1.—Effect of Administering Pituitary Extract and Histamin by Various Routes

Method	Urine per Hour				
	Before	After Administration			
	I	II	III	IV	V
No Antidiuretic Effect:					
2 c.c. pituitrin "O" by mouth	450	435	440	255	455
4 c.c. pituitrin "O" by rectum	425	510	225	325	500
1 c.c. histamin, 1:10,000, subcutaneously	540	500	436	400	427
Marked Antidiuretic Effect:					
0.25 c.c. pituitrin "O" subcutaneously	500	55	45	130	315
1.0 c.c. pituitrin "O" subcutaneously	350	95	20	150	325
0.5 c.c. oral pituitary extract, intranasally	410	45	360	510	570
5 c.c. oral pituitary extract, intranasally	335	75	95	140	455

In order to determine the efficacy of these measures in reducing the twenty-four hour intake and output, the patient was encouraged to drink all the water necessary for comfort. The fluid intake and output were carefully measured. The same diet was continued. One and five-tenths c.c. of oral pituitary extract was sprayed intranasally every three hours on one day (Column 2, Chart 2), and every four hours

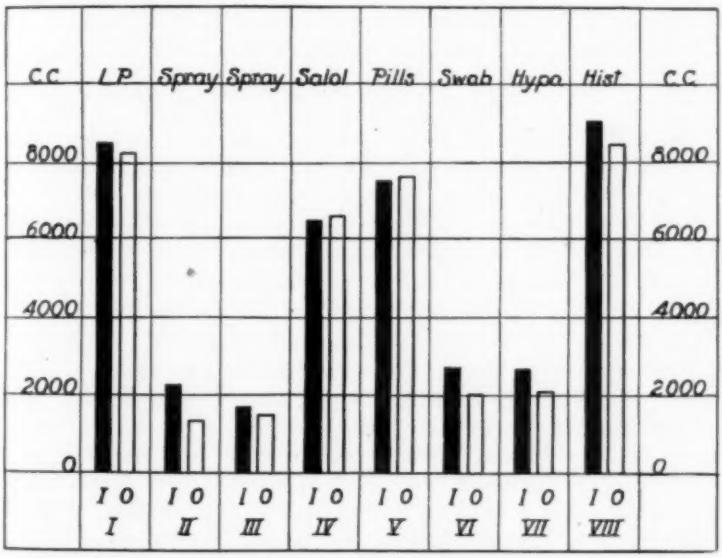


Chart 2.—Comparative effect of various measures on twenty-four hourly fluid intake and output. I. Indicates fluid intake; O, urinary output. I. Effect of lumbar puncture. II. Intranasal spray of 1.5 c.c. oral pituitary extract every three hours. III. Intranasal spray of 1.5 c.c. oral pituitary extract every four hours. IV. Phenyl salicylate coated tablets, 1.3 gm. V. Posterior lobe pituitary pills (Burroughs Wellcome Co.) 0.13 gm. every four hours. VI. Swab soaked in 1 c.c. pituitrin "O" inserted in one nostril and changed every four hours. VII. Subcutaneous injection of 0.5 c.c. pituitrin "O" every six hours. VIII. Histamin, 1 c.c. 1:10,000 solution (Parke, Davis & Company) injected subcutaneously every six hours.

on the next day (Column 3), with marked decrease in urinary output. A cotton plug soaked with 1 c.c. of pituitrin "O" was introduced into one nostril at four hour intervals with essentially the same result (Column 6). Pituitary extract was then withheld and after the patient had returned to his usual intake and output level, phenyl salicylate coated tablets (Column 4), and posterior lobe pituitary tablets (Burroughs Wellcome Co.), (Column 5), were administered by mouth.

The results are graphically represented in Chart 2.

Changes in Blood Concentration.—An attempt was made to determine what changes, if any, occurred in the concentration of the blood serum before and after intranasal administration of pituitary extract. The patient was allowed an unlimited intake of fluid. Two specimens of blood were taken at hourly intervals, after which 4 c.c. of pituitrin "O" was sprayed intranasally. Samples of blood were taken at the end of one-half hour, one hour, two hours and three hours. The protein concentration of the blood was determined by the refractometer. That this is both exceedingly sensitive and reliable as an index of blood concentration has been demonstrated by Reiss.[8]

TABLE 2.—Changes in Blood Concentration Before and After Intranasal Administration of Pituitary Extract

Time	Percentage of Concentration	Urine (Water ad lib.)
9	9.25	420
10	9.25	95
10:30	9.25	0
11	8.96	18
12	....	46
1	8.0	33

Metabolism.—The possible effect of pituitrin on the metabolic rate was also investigated. The patient's basal metabolism was therefore determined on four occasions by the Tissot method, two determinations which checked within 4 per cent. being made each time. The normal standards of Aub and DuBois for calories per square meter of body surface (height-weight formula) per hour were used, and the results expressed in per cent. of normal. The determinations were made after a fourteen hours' fast, on two occasions after the administration of pituitary extract and on two other occasions without any medication.

The results were as follows: Dec. 15, 1921, —4; December 31, —26; Jan. 9, 1922, —20; January 13, —23. The relatively high result of the first determination was probably due to the patient's restlessness, associated with thirst and a desire to void. The second and third determinations were made immediately following pituitary extract

8. Reiss: Arch. f. exper. Path. u. Pharmakol. **51**:18, 1903.

sprays with the patient perfectly comfortable and quiet. The fourth determination was done two days after pituitary extract was discontinued, when his daily intake and output were 8,600 c.c. and 8,400 c.c., respectively. Prior to the first three determinations the patient had been deprived of water for approximately three hours, but on this fourth occasion he was permitted small amounts of warmed water at room temperature until one hour before the metabolic rate was determined. As a result, the patient was not restless and the metabolic rate was determined under more satisfactory conditions.

The foregoing results do not indicate any marked pituitary extract effect on the metabolic rate. Whether the lowered metabolism in this case bears any relation to the syndrome of diabetes insipidus, or whether it is due entirely to the malnutrition of the patient,[9] it is impossible to say.

DISCUSSION

Extract of the posterior lobe of the pituitary sprayed intranasally checked both the polyuria and polydipsia as effectively as hypodermic injections. All administrations of dried or aqueous extracts by mouth or rectum proved ineffectual, this being in accord with the results of practically all previous observers.

Histamin, whether sprayed, swallowed or injected subcutaneously, failed to modify the thirst or polyuria. One c.c. of a 1 : 10,000 solution injected subcutaneously did not cause any toxic symptoms. The preparation used was shown by Dale's method to be physiologically active in concentrations of 1 : 10,000,000.

Lumbar puncture, performed on two different occasions, did not lower the water or urinary output as it did in the cases reported by Herrick [10] and Graham.[11]

The effect of pituitary extract intranasally and subcutaneously was a diminution of the water intake and urinary output with a corresponding alleviation of thirst, a rise in the specific gravity of the urine and a dilution of the blood. The dilution of the blood has also been noted by Konschegg and Shuster [12] and by Priestly.[13]

Whether intranasal sprays will be as successful in other cases, is, of course, impossible to state, for it is conceivable that the efficacy of the method in this instance was due to the small amount of pituitary extract that the patient required.

The exact mechanism underlying the nasopharyngeal absorption is not clear. Certain facts are, however, of considerable interest in this

9. Benedict, Francis G., Miles, Victor R., Rath, Pane, Smith, H., Monmouth: Publication No. 280, Carnegie Institution of Washington, 1919, p. 694.
10. Herrick: Arch. Int. Med. **10**:1 (July) 1912.
11. Graham: J. A. M. A. **69**:1498 (Nov. 3) 1917.
12. Konschegg and Shuster: Deutsch. Med. Wchnschr. **51**:1091, 1915.
13. Priestly, J. G.: J. Physiol. **55**:305, 1921.

connection. "That the lymphatics of the nasal mucosa are in almost direct communication with the subarachnoid space has been clearly demonstrated," [14] and clinically, in children, a surprisingly small patch of inflammation in the nasopharynx excites convulsions, stupor and other phenomena indicative of considerable cerebral irritation.[15] Flexner [16] has shown that after intraspinal inoculation of monkeys with the *Diplococcus Intracellularis*, the organisms can be detected both free and intracellularly in the nasopharynx; and similarly, the virus of poliomyelitis has been demonstrated in the nasal mucosa of monkeys inoculated intraspinally.[17] The successful inoculation of poliomyelitis virus into the nasopharynx of monkeys, clearly demonstrating that the nasopharynx may serve as a portal of entry, is also suggestive in this connection.[18]

The preceding evidence indicates that the nasopharynx constitutes an important factor in certain diseased states, but whether absorption in the present instance is accomplished by the blood stream, by the lymphatics, or by both channels, it is impossible to state.

CONCLUSIONS

1. In a case of diabetes insipidus under observation, extract of the posterior lobe of the pituitary applied intranasally checked both the polyuria and polydipsia as effectively as hypodermic injection.

2. Histamin, subcutaneously; lumbar puncture, and pituitary extract by mouth, by rectum, and by phenyl salicylate coated tablets, proved ineffectual.

NOTE.—After this paper had been written, three additional cases of diabetes insipidus were studied. In each instance intranasal application of pituitary extract was found to be fully as satisfactory as hypodermic injection in reducing the fluid intake and urinary output to an approximately normal level.

14. Peabody, Draper and Dochez: A Clinical Study of Acute Poliomyelitis, Monograph of the Rockefeller Institute for Medical Research, No. 4, June 1, 1912, p. 12.

15. Schloss, O.: Personal communication.

16. Flexner, S.: J. A. M. A. **55**:1105 (Sept. 24) 1910.

17. Flexner, S., and Lewis, P. A.: J. A. M. A. **54**:535 (Feb. 12) 1910.

18. Landsteiner, K., and Levaditi, C.: Ann. de l'Inst. Pasteur **24**:833, 1910.

THE VITAL CAPACITY IN A GROUP OF COLLEGE STUDENTS*

A. W. HEWLETT, M.D., AND N. R. JACKSON, M.D.
SAN FRANCISCO

The lessened vital capacity in intrathoracic diseases and the recommendation that vital capacity be used as a test of physical fitness have renewed interest in the question of normal standards for vital capacity. The vital capacity varies greatly even among healthy individuals, and some of the factors which accompany these variations are known. Among them are the sex, weight, height, size of the chest, age and general physical fitness. The clinician desires a normal standard with which he may compare the vital capacity of his patient. Would he do better, for example, to compare it with the average for individuals of the same height, of the same weight or of the same chest measurements; or should he use some combination of these? Obviously, that standard is best which shows the least variation among normal individuals. The convenience of the standard also deserves some consideration, for a convenient standard is more likely to be generally used.

Hutchinson [1] after examining about 3,000 men came to the conclusion that the most reliable standard for estimating the vital capacity of men was their standing height. He stated that on the average the vital capacity increased 8 cubic inches of air for every inch increase of height between the heights of 5 and 6 feet. According to Hutchinson the vital capacity increased also with the weight, but this occurred only up to an average weight of about 155 pounds. Increases of weight beyond this were not, on the average, accompanied by increased vital capacity. According to Hutchinson also the vital capacity tended to grow less after the age of about 33 years, although the chest circumference showed a slight tendency to grow greater. Peabody and Wentworth [2] grouped their normals into three classes according to height. This method has an obvious disadvantage in the case of those whose heights lie near the class borders, for they are compared with a standard that is best suited for a different height. Lundsgaard and Van Slyke [3] compared the vital capacity with certain chest dimensions;

* From the Department of Medicine, Leland Stanford Junior University.

1. Hutchinson, J.: On the Capacity of the Lungs, and on the Respiratory Functions, with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, Med. Chir. Tr. Lond. **29**:139, 1846.

2. Peabody, F. W., and Wentworth, J. A.: Clinical Studies on Respiration, Arch. Int. Med. **20**:443 (Oct.) 1917.

3. Lundsgaard, C., and Van Slyke, D. R.: Relation Between Thorax Size and Lung Volume, J. Exper. M. **27**:65, 1918.

but West [4] found a poor correlation between these dimensions and the vital capacity of his subjects. Dreyer [5] compared the vital capacity with the weight, the stem height (measured from the top of the head to the end of the sacrum) and the circumference of the chest. So far as weight was concerned, Dreyer neglected this in individuals whose weight did not correspond to their stem height; so that for practical purposes his comparisons were based on the stem height and the circumference of the chest. Finally West [4] compared the vital capacity with the surface area, as calculated from the height and weight by the DuBois' formula.[6]

Our observations were made on 400 normal young men at Leland Stanford Jr. University between the ages of 18 and 30. All of these were active and showed no evident signs of disease. In each case the height was taken in bare feet and the weight was stripped weight. The vital capacity was determined by a spirometer which gave accurate readings. Each individual was first shown how the test was performed and was then given three trials. The highest of the three readings was recorded as his vital capacity. The body surface area was estimated from the height and weight by using the diagram of DuBois and DuBois. Unfortunately, neither the sitting height nor the stem height according to Dreyer were taken. The individual observations are shown in Table 1.

A general conception of the relation between the vital capacities and weights of our students may be gained from Figure 1. The observations were grouped according to weights, and the average vital capacity for each weight group was determined. These averages increased with increasing weights but the rate of increase was relatively rapid at low weights and relatively slow at high weights. Hutchinson noted a similar change at the higher weights. In his statistics, however, the change at higher weights was more marked. We are inclined to attribute this difference to the fact that Hutchinson's observations included men of all ages. The excess fat so often accumulated as a person grows older is probably accompanied by no corresponding increase in vital capacity. Dreyer stated that the vital capacity is proportional to the 0.72 power of the weight ($W + ^{0.72}$). Dreyer's line representing this relationship is curved in the general direction of our averages; but the curve for the weights here under consideration is hardly appreciable. For the sake of comparison we have inserted

4. West, H. F.: Clinical Studies on Respiration; Comparison of Various Standards for Normal Vital Capacity of Lungs, Arch. Int. Med. **25**:306 (March) 1920.

5. Dreyer, G.: The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

6. DuBois, D., and DuBois, E. F.: Clinical Calorimetry. Fifth Paper. The Measurement of the Surface Area of Man, Arch. Int. Med. **15**:868 (June) 1915.

TABLE 1.—VITAL CAPACITY OF GROUP OF COLLEGE STUDENTS

Vital Capacity	Height	Weight	Surface Area	Vital Capacity	Height	Weight	Surface Area
6,700	187.0	80.4	2.06	5,277	181.1	93.2	2.14
6,555	186.7	75.7	1.98	5,244	173.3	63.6	1.77
6,555	198.7	87.7	2.17	5,200	180.0	67.2	1.86
6,655	189.2	82.3	2.07	5,200	175.5	61.5	1.76
6,500	195.5	85.6	2.18	5,200	175.3	65.0	1.78
6,200	180.5	79.0	1.99	5,200	174.5	64.4	1.78
5,981	185.4	77.3	1.98	5,161	187.0	77.3	2.01
5,981	184.0	94.1	2.14	5,114	178.0	71.4	1.88
5,809	172.0	70.5	1.83	5,163	182.8	78.2	2.01
5,860	187.2	65.0	1.87	5,163	171.6	60.5	1.81
5,899	185.4	75.0	1.95	5,163	171.0	67.3	1.76
5,817	172.7	70.9	1.82	5,150	170.5	64.4	1.75
5,800	179.5	71.6	1.90	5,100	174.0	61.6	1.75
5,760	185.0	77.0	2.03	5,081	175.9	64.5	1.80
5,736	180.0	60.5	1.77	5,081	182.9	72.7	1.92
5,736	180.0	76.4	1.95	5,081	176.0	66.4	1.78
5,736	180.3	90.0	2.10	5,081	184.0	80.4	2.08
5,736	184.0	78.2	2.00	5,074	174.0	72.7	1.88
5,736	181.2	68.2	1.95	5,065	172.0	65.0	1.77
5,752	191.0	79.5	2.08	5,031	183.0	70.0	1.90
5,736	180.3	72.7	1.90	5,081	182.5	70.5	1.90
5,736	187.9	65.0	1.88	5,073	172.0	78.1	1.92
5,700	174.5	72.4	1.87	5,081	174.0	79.5	1.94
5,700	186.0	70.2	1.93	5,081	187.0	69.1	1.94
5,637	184.0	76.8	1.96	5,081	180.6	82.3	2.01
5,654	185.0	68.7	1.92	5,081	176.0	78.6	1.95
5,572	185.4	79.5	2.03	5,081	188.0	84.1	2.06
5,572	185.4	82.3	2.05	5,077	180.0	70.9	1.89
5,572	188.1	78.2	2.06	5,031	179.0	81.0	1.98
5,572	191.0	94.0	2.24	5,000	179.5	65.2	1.83
5,572	190.5	92.2	2.20	5,000	175.0	78.5	1.94
5,572	185.3	78.2	2.03	5,000	173.0	64.3	1.78
5,572	182.8	75.0	1.96	5,000	183.0	75.2	1.97
5,571	173.0	71.4	1.83	5,000	170.8	64.1	1.75
5,505	184.0	63.6	1.85	4,916	175.5	70.5	1.85
5,500	179.0	64.6	1.82	4,998	167.6	65.0	1.74
5,450	177.7	70.6	1.88	4,916	180.3	67.3	1.84
5,490	179.1	63.6	1.83	4,916	172.0	67.0	1.77
5,490	185.4	84.0	2.07	4,916	184.0	64.5	1.85
5,407	170.0	77.3	1.87	4,916	173.0	63.6	1.77
5,407	186.5	85.0	2.10	4,916	170.0	71.8	1.82
5,407	187.2	72.7	1.95	4,916	180.0	65.9	1.84
5,407	188.0	71.4	1.96	4,916	172.5	70.0	1.83
5,410	178.1	79.5	1.98	4,949	185.6	66.8	1.87
5,420	189.0	83.2	2.07	4,916	172.5	69.0	1.83
5,415	180.3	77.5	1.95	4,916	185.6	74.1	1.97
5,488	177.8	62.3	1.76	4,982	184.0	72.7	1.96
5,407	177.0	60.0	1.75	4,952	190.0	78.1	2.06
5,405	177.5	58.2	1.76	4,900	185.0	73.2	1.94
5,325	185.3	84.1	2.08	4,916	173.2	79.5	1.93
5,325	181.8	84.1	2.04	4,916	183.6	71.4	1.92
5,320	178.0	60.5	1.76	4,916	182.8	84.1	2.06
5,325	185.3	70.0	1.93	4,998	177.8	63.0	1.81
5,325	175.2	65.9	1.79	4,916	181.5	71.0	1.89
5,338	181.0	70.5	1.89	4,900	177.8	66.7	1.83
5,300	180.0	64.1	1.83	4,916	178.3	70.0	1.87
5,340	170.0	70.3	1.81	4,916	177.8	60.5	1.75
5,325	180.3	68.0	1.87	4,998	180.3	61.0	1.77
5,300	181.0	80.8	2.01	4,916	179.0	74.0	1.93
5,300	168.0	63.2	1.72	4,998	179.0	67.8	1.87
5,300	181.5	70.4	1.90	4,916	174.8	79.5	1.95
5,300	181.8	74.4	1.95	4,916	168.5	66.9	1.76
5,244	185.4	72.7	1.94	4,960	168.8	65.0	1.73
5,244	175.9	64.5	1.79	4,900	169.0	66.0	1.77
5,244	179.0	63.0	1.83	4,900	169.0	72.0	1.83
5,244	173.9	66.6	1.84	4,900	172.5	68.2	1.81
5,244	173.0	64.0	1.76	4,850	179.0	63.6	1.80
5,211	184.0	70.0	1.91	4,850	175.8	67.8	1.83
5,235	174.0	94.0	2.06	4,850	175.0	60.5	1.74
5,244	175.5	80.0	1.95	4,800	171.0	65.0	1.77
5,244	177.0	69.1	1.86	4,800	178.0	65.2	1.82
5,260	178.1	71.8	1.88	4,834	175.4	68.2	1.84
5,244	180.6	80.0	2.00	4,850	186.5	82.7	2.07
5,244	185.6	72.7	1.96	4,824	184.0	92.0	2.14
5,244	185.0	66.9	1.91	4,824	175.2	70.0	1.85
5,244	188.0	77.7	2.06	4,741	172.7	67.3	1.78
5,244	174.0	77.7	1.94	4,734	175.9	75.9	1.91
5,244	167.6	58.2	1.68	4,752	172.0	63.6	1.76
5,277	184.0	70.5	1.92	4,752	184.0	69.1	1.91
5,252	176.0	72.3	1.86	4,732	173.0	71.8	1.84
5,244	180.8	76.3	1.95	4,752	180.3	70.5	1.89

TABLE 1.—Vital Capacity of Group of College Students—(*Continued*)

Vital Capacity	Height	Weight	Surface Area
4,752	170.0	67.5	1.80
4,734	170.0	68.2	1.80
4,752	173.0	65.0	1.77
4,788	187.2	77.3	2.00
4,700	173.0	64.0	1.76
4,752	176.0	68.0	1.85
4,752	184.0	78.1	2.02
4,734	178.0	70.0	1.87
4,752	173.0	65.4	1.78
4,752	183.0	70.0	1.91
4,752	185.4	77.7	2.08
4,752	182.8	79.5	2.02
4,752	189.0	68.2	1.95
4,752	173.0	68.2	1.84
4,752	181.0	82.3	2.00
4,746	183.0	84.1	2.06
4,752	186.5	68.5	1.94
4,760	175.7	82.7	1.99
4,760	175.6	60.0	1.74
4,752	181.0	66.9	1.86
4,750	176.0	66.0	1.81
4,700	176.0	60.2	1.74
4,700	177.0	74.2	1.91
4,700	178.0	62.4	1.78
4,700	171.0	63.5	1.75
4,700	182.0	70.5	1.91
4,700	169.0	74.4	1.85
4,670	175.9	67.3	1.81
4,670	172.7	67.3	1.79
4,670	180.3	68.2	1.88
4,670	180.3	66.4	1.84
4,600	180.0	72.7	1.92
4,670	170.0	64.5	1.75
4,600	166.0	63.2	1.69
4,670	175.4	60.0	1.74
4,670	184.0	94.5	2.18
4,626	174.0	81.2	1.94
4,670	185.3	70.5	1.93
4,612	175.2	72.3	1.85
4,662	179.0	63.0	1.82
4,670	175.2	65.9	1.79
4,650	170.4	63.6	1.74
4,600	174.0	68.0	1.82
4,600	173.5	65.2	1.79
4,600	173.5	68.9	1.84
4,588	175.9	60.5	1.75
4,588	182.9	60.5	1.79
4,588	170.2	60.5	1.70
4,588	170.0	67.5	1.78
4,588	177.2	114.5	2.29
4,506	180.0	67.3	1.85
4,588	176.0	68.6	1.86
4,506	178.0	72.7	1.93
4,588	182.5	72.7	1.92
4,580	176.0	68.2	1.86
4,572	171.0	64.5	1.76
4,580	182.0	66.0	1.84
4,588	180.5	76.8	1.96
4,572	183.1	69.1	1.90
4,506	173.8	66.4	1.78
4,580	189.0	78.2	2.06
4,506	183.0	78.0	2.01
4,597	173.1	70.0	1.82
4,500	187.0	67.3	1.92
4,506	176.0	80.4	1.96
4,500	174.0	86.8	2.02
4,506	173.8	68.2	1.84
4,588	180.3	74.0	1.94
4,588	181.5	70.5	1.89
4,580	180.3	77.2	1.96
4,506	178.0	72.3	1.88
4,539	180.0	68.2	1.88
4,506	163.0	60.5	1.75
4,506	175.2	70.9	1.85
4,588	180.3	65.9	1.82
4,588	173.5	71.4	1.84
4,520	174.0	57.0	1.69
4,500	167.0	62.5	1.70
4,500	187.5	57.6	1.79
4,500	170.0	53.5	1.62
4,500	164.3	62.2	1.68

Vital Capacity	Height	Weight	Surface Area
4,425	187.2	79.5	2.05
4,425	175.8	68.2	1.85
4,425	179.0	62.8	1.82
4,425	172.0	60.5	1.71
4,420	172.7	67.3	1.77
4,416	170.0	71.8	1.82
4,425	184.0	72.7	1.94
4,425	174.0	78.0	1.94
4,425	170.0	79.5	1.92
4,425	180.3	90.9	2.10
4,425	168.2	55.0	1.63
4,416	175.0	84.5	2.00
4,425	177.4	68.7	1.86
4,457	170.0	66.9	1.78
4,440	178.0	78.2	1.97
4,409	166.5	56.0	1.62
4,463	169.9	58.6	1.69
4,425	169.0	59.1	1.69
4,440	172.5	72.3	1.83
4,450	173.8	57.6	1.69
4,400	161.5	59.5	1.63
4,400	173.5	64.8	1.78
4,400	177.8	71.6	1.89
4,400	183.0	70.8	1.92
4,343	176.0	65.5	1.80
4,343	170.1	60.5	1.70
4,343	162.0	64.5	1.69
4,343	175.7	74.5	1.90
4,343	168.0	66.4	1.76
4,350	163.2	60.0	1.65
4,300	169.0	67.4	1.78
4,300	174.0	57.2	1.69
4,300	179.0	60.2	1.77
4,300	167.5	58.8	1.67
4,300	166.0	64.8	1.72
4,251	168.0	67.5	1.78
4,250	176.0	60.0	1.70
4,250	169.0	60.5	1.69
4,250	162.0	63.2	1.64
4,251	180.0	67.8	1.87
4,251	170.1	63.6	1.75
4,251	176.4	87.7	2.06
4,211	176.0	69.1	1.85
4,250	172.6	88.8	2.06
4,250	165.0	65.0	1.73
4,211	173.0	75.0	1.88
4,251	177.0	60.0	1.75
4,251	167.6	56.0	1.63
4,250	178.0	68.7	1.87
4,242	170.0	61.8	1.72
4,245	174.0	60.5	1.73
4,250	173.6	64.5	1.77
4,250	166.5	57.7	1.66
4,250	178.0	68.2	1.87
4,250	164.0	64.5	1.72
4,250	172.5	62.2	1.74
4,210	180.2	55.5	1.71
4,200	175.6	65.8	1.81
4,200	167.5	51.4	1.57
4,200	172.0	57.3	1.68
4,200	165.0	56.3	1.62
4,200	171.0	57.4	1.67
4,100	186.0	60.0	1.82
4,179	160.0	64.5	1.68
4,170	172.6	81.2	1.94
4,170	177.8	67.3	1.85
4,180	173.5	62.7	1.77
4,180	181.5	70.5	1.89
4,180	170.0	64.5	1.75
4,100	171.5	57.0	1.67
4,100	174.0	64.0	1.78
4,087	172.7	54.4	1.65
4,087	179.1	60.4	1.77
4,080	168.9	54.5	1.63
4,087	180.3	61.8	1.78
4,087	172.0	60.5	1.72
4,080	176.0	67.3	1.83
4,087	176.0	62.7	1.77
4,087	183.0	75.6	1.97
4,070	162.0	60.0	1.64
4,087	172.6	57.3	1.68

TABLE 1.—VITAL CAPACITY OF GROUP OF COLLEGE STUDENTS—(*Continued*)

Vital Capacity	Height	Weight	Surface Area	Vital Capacity	Height	Weight	Surface Area
4,087	171.2	53.2	1.60	3,750	160.0	70.5	1.73
4,095	176.4	62.3	1.75	3,760	162.5	57.5	1.59
4,015	173.4	71.4	1.84	3,730	163.0	84.5	1.90
4,050	170.1	80.4	1.92	3,709	165.0	57.7	1.66
4,015	170.0	55.4	1.64	3,750	175.5	58.8	1.72
4,015	165.0	54.6	1.60	3,750	168.5	56.5	1.64
4,087	168.2	62.6	1.73	3,605	172.6	59.1	1.70
4,087	164.0	64.5	1.71	3,605	157.4	47.3	1.46
4,050	166.3	59.8	1.67	3,687	172.6	68.2	1.82
4,050	172.0	57.3	1.68	3,687	162.5	60.0	1.64
4,050	172.2	60.9	1.72	3,605	177.8	57.0	1.74
4,050	172.5	55.9	1.67	3,687	185.0	58.4	1.79
4,000	169.5	60.0	1.69	3,687	173.0	59.1	1.72
4,000	173.6	58.7	1.70	3,605	172.0	60.0	1.72
3,900	172.7	60.5	1.72	3,588	167.6	65.9	1.75
3,982	168.3	60.4	1.68	3,675	171.0	66.9	1.77
3,900	176.0	63.6	1.80	3,925	170.0	55.9	1.64
3,933	180.0	77.3	1.96	3,687	179.0	62.2	1.77
3,933	173.0	58.2	1.70	3,687	175.2	58.9	1.66
3,900	180.3	74.5	1.94	3,605	171.0	66.9	1.78
3,933	158.7	60.0	1.63	3,650	160.7	57.3	1.60
3,960	169.0	62.7	1.73	3,600	157.5	62.0	1.63
3,933	168.0	75.9	1.86	3,500	162.8	56.0	1.60
3,933	170.5	59.1	1.70	3,400	166.9	58.0	1.65
3,950	169.0	58.8	1.68	3,441	180.3	68.2	1.78
3,910	174.5	72.0	1.87	3,441	166.0	65.4	1.74
3,900	160.6	58.4	1.55	3,450	167.0	65.0	1.74
3,900	167.0	62.5	1.70	3,425	187.0	59.1	1.83
3,851	182.8	67.8	1.90	3,441	170.1	60.0	1.70
3,842	172.6	65.3	1.77	3,472	170.1	75.9	1.82
3,851	167.8	56.8	1.64	3,250	169.5	58.2	1.69
3,801	176.6	64.5	1.79	3,277	176.0	61.0	1.75
3,802	179.0	68.2	1.81	3,290	168.0	52.3	1.57
3,769	172.0	67.5	1.78	3,277	160.8	63.6	1.65
3,769	179.0	60.4	1.76	3,277	164.3	52.7	1.55
3,769	168.9	70.7	1.81	3,150	167.0	66.9	1.77
3,769	170.0	58.2	1.68	3,115	165.0	62.6	1.69
3,769	179.3	58.6	1.76	3,048	175.5	60.0	1.74

in Figure 1 the straight line relationship between weight and vital capacity as calculated from our data, Dreyer's line, and Hutchinson's averages of vital capacity for different weight groups. The lower averages in Hutchinson's statistics will be considered farther on.

Figure 2 indicates for our students the average vital capacities of the different height groups. We have added the similar averages of Hutchinson's cases, the straight line relationship between vital capacity and height as calculated from our data and the straight line relationship which Hutchinson proposed for his. Both in our cases and in those of Hutchinson the relationship between the height and the vital capacity for height groups approached a straight line.

The statistical methods employed are based on two assumptions. The first is that the relationship between the factors compared approaches a straight line relationship. We have shown that this is approximately the case so far as the relation between height and vital capacity is concerned. The relation between weight and vital capacity deviates somewhat from a straight line in the case of our students and this deviation is quite marked in Hutchinson's observations. The second assumption is that the data for each group of observations approximates the so-called normal distribution curve. This is true of

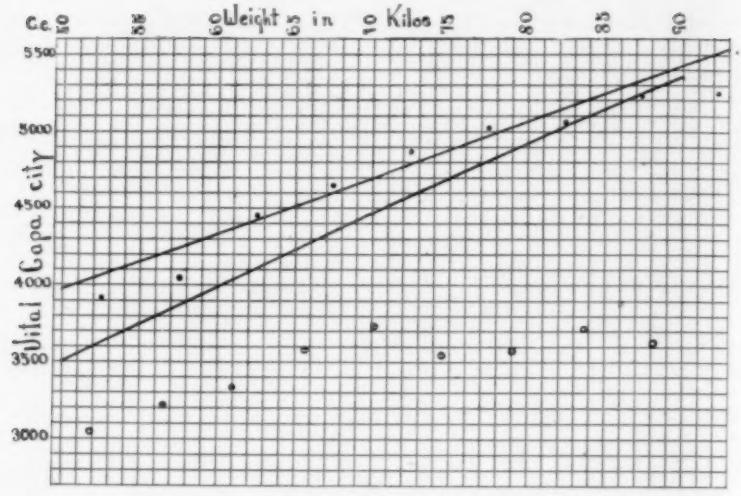


Fig. 1.—The vital capacity and weight. The dots represent the average vital capacities for different weight groups of Stanford students. The circles represent similar averages for Hutchinson's cases. The upper straight line is the calculated line for Stanford students. The line just below is Dreyer's line. Its curve is hardly perceptible.

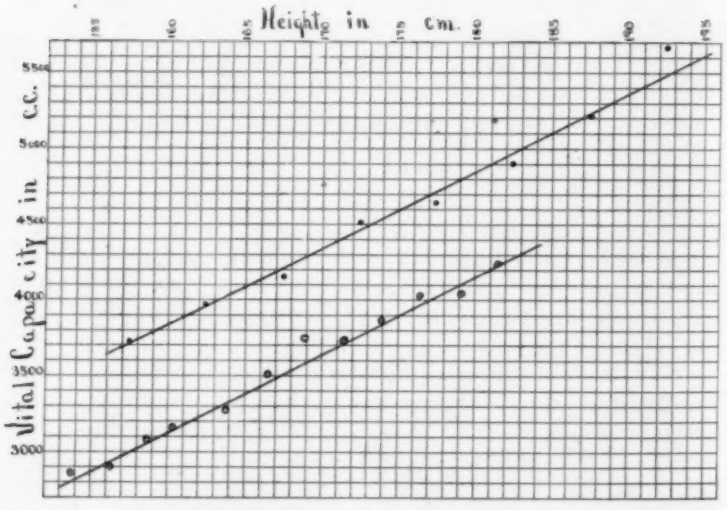


Fig. 2.—The vital capacity and height. The dots represent the average vital capacities for different height groups of Stanford students. The circles represent similar averages for Hutchinson's cases. The upper straight line is the calculated line for Stanford students. The lower straight line is that proposed by Hutchinson.

biologic measurements in general, including height and weight. It is also true of the vital capacity. Figure 3 shows the actual observations in Stanford students and the calculated theoretical distribution curve.

With the above assumption it is possible by the mathematical methods employed in statistical studies to determine the relation of vital capacity to height, to weight and to their combination. For determining these relations in college students we have used our figures on 400 Stanford students, the figures of West on eighty-five Harvard medical students and the figures of Schuster [7] on 959 Oxford students. For comparison, Hutchinson's data on 1,285 men as shown in his Table D have also been used. We have calculated from these data the standard deviations, the coefficients of correlation, and the formulas which best express the straight line relationship between vital capacity

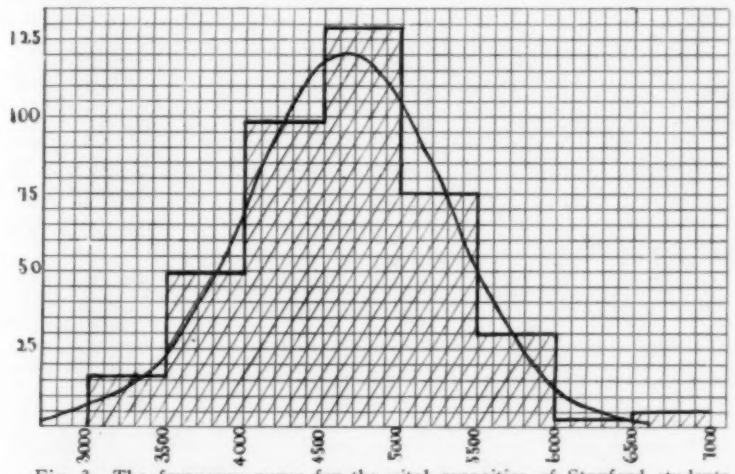


Fig. 3.—The frequency curve for the vital capacities of Stanford students. The shaded columns represent the number of observations between different limits of vital capacity. The curve represents the theoretical distribution as calculated from the standard deviation, the mean, and the total number of observations.

and various other factors. The methods used are described in Yule's "Introduction to the Theory of Statistics."

Briefly, it may be stated that the standard deviation expresses the dispersion of the data on either side of the average. It is expressed by the formula $\sigma = \sqrt{\frac{\Sigma x^2}{N}}$ where σ is the standard deviation, x is the deviation of any one point from the average, Σx^2 is the sum of the squares of these individual deviations, and N is the number of observations.

7. Schuster, E.: First Results from the Oxford Anthropometric Laboratory, Biometrika **8**:40, 1911.

The coefficient of correlation, r, indicates how closely the observations of any two sets of data on the same individuals, e. g. vital capacity and height, range themselves about a straight line relationship. It is calculated from the formula $r = \frac{\Sigma xy}{N\sigma x\sigma y}$ where x and y represent the deviations of each point from the averages of x and y, respectively, Σxy the sum of the products of these deviations, N the number of observations and σx and σy the standard deviations of the two groups of observations that are being compared, e. g., vital capacity and height. The more nearly r approaches unity the more closely do the data range themselves on a straight line, i. e., the more exact is the linear correlation. A mathematical expression for the line of relationship is given by the formula $y = a + r\frac{\sigma y}{\sigma x}x$ where for example, y represents the vital capacity, x the height, r the coefficient of correlation between height and vital capacity, σy the standard deviation of the vital capacity, σx the standard deviation of the height and a is a constant. The standard deviation of the individual observations from this calculated line is represented by the expression $\sigma y\sqrt{1 - r^2}$.

TABLE 2.—Results of Comparison of Data from Three Groups of Students

	Oxford	Harvard	Stanford	S. & H.	S. H. & O.	Hutchinson
Number	999	85	400	485	1,444	1,285
Means:						
Weight	68.52	64.50	68.49	.....	68.28	68.30
Height	176.5	172.6	175.9	.....	176.2	171.5
Vital capacity	4,315	4,051	4,640	4,647	4,426	3,602
Surface area	.....	1.776	1.835	1.825	.....	.....
Standard Deviations:						
Weight	7.425	7.176	8.831	.....	7.885	8.796
Height	6.606	6.856	7.121	.....	6.805	6.637
Vital capacity	613.2	652.5	655.8	655.3	646.9	(446.3)*
Surface area	.....	0.1167	0.1332	0.1324	.....	.....
Coefficients of Correlation:						
Wt. : Ht.	0.66	0.61	0.50	.....	0.60	0.00
Wt. : V. C.	0.50	0.67	0.49	.....	0.53	(0.63)*
Ht. : V. C.	0.57	0.63	0.56	.....	0.53	(0.86)*
S. A. : V. C.	.....	0.73	0.57	0.59	.....	.....

* Calculated from Hutchinson's averages as given in his Table D. The use of averages makes the standard deviation too small and the coefficients of correlation too large.

Table 2 gives the results obtained by these statistical calculations. In the group studied by Hutchinson, which comprised men of different ages and different occupations, the average weight was the same as the average weight of the college students, whereas the average height was definitely less. On the average, then, Hutchinson's subjects were somewhat shorter and relatively fatter than our students. The average vital capacity differed considerably in the different groups. The Stanford and Harvard medical students showed the highest average vital capacity; the Oxford average was about 7 per cent. lower and Hutchinson's average group was more than 20 per cent. lower. This low average in Hutchinson's group was probably due, in part, to the fact that he studied men of all classes and all ages, whereas college students represent a picked class both as to age and general physical fitness. It seems unlikely, however, that the low average in Hutchinson's group was due entirely to this cause. Difference in technic or in the instruments used may have been partly responsible for his low figures.

Fluctuations on either side of the average are indicated by the standard deviations given in Table 2. These fluctuations were greater among the Stanford students than among the Oxford or the Harvard medical students. In all groups the fluctuations of vital capacity were relatively greater than the fluctuations of either weight or height. Thus for all students the standard deviation for vital capacity amounted to 14.6 per cent. of the mean, the standard deviation for weight amounted to 11.5 per cent. of the mean, and the standard deviation for height amounted to 3.9 per cent. of the mean. It is evident, therefore, both from the different averages and from the standard deviations that the vital capacity of normal individuals shows a rather wide range of fluctuation.

Table 2 shows also that among college students the correlation between weight and vital capacity is approximately the same as the correlation between height and vital capacity. Hutchinson did not record the individual vital capacities of his subjects and it is not possible from his data properly to calculate correlation coefficients for vital capacity and either weight or height. We have, however, made such calculations from the average vital capacities given in his Table D. From these it is evident, as he stated and as is shown in our Figures 1 and 2, that for his cases the correlation of vital capacity with height is far better than the correlation with weight. This difference between college men and men at large with respect to the correlation of weight and vital capacity may be explained on the assumption that the latter group includes some fat men whose excess weight is accompanied by no increase or perhaps by a decrease of vital capacity. It seems to us, therefore, that weight is not a reliable index of vital capacity unless one can exclude those with excess fat.

Among college students, where excess fat is not common, there is a closer correlation between vital capacity and a combination of weight and height than between vital capacity and either height or weight alone. West proposed that the body surface as calculated from the weight and height be used as an index of vital capacity and it may be seen from Table 2 that the correlation with body surface is somewhat better than the correlation with either height or the weight alone. A combination of the linear relationships of vital capacity to weight and to height was calculated. This correlation will be discussed later.

By applying the methods of statistical study to the above data, formulas may be obtained by means of which one may calculate for college students the probable vital capacity either from the height, from the surface area, or from the linear combination of height and weight. The first and last formulas are based on the combined Stanford, Oxford and Harvard medical statistics. The second is based on the correlation

coefficient between vital capacity and surface area of the Stanford and the Harvard medical groups and on the average for all students. The formulas obtained are as follows:

$$VC = 50\ Ht - 4{,}400$$
$$VC = 2{,}900\ SA - 1{,}000$$
$$VC = 27\ Wt + 31.5\ Ht - 3{,}000$$

In these formulas vital capacity is expressed in cubic centimeters, height in centimeters, surface area in square meters and weight in kilograms.

The standard deviations of the observed vital capacities of students from vital capacities which have been calculated from the above formulas are as follows:

Standard deviation of vital capacities from height formula, 548.6 c.c.

Standard deviation of vital capacities from surface area formula, 529.1 c.c.

Standard deviations of vital capacities from weight and height formula, 521.1 c.c.

TABLE 3.—Showing Number of Students Out of Each Hundred Who May Be Expected to Have a Vital Capacity Which Falls Below the Following Percentages of Their Calculated Vital Capacity, When the Different Formulas Are Used

	Falling Below				
	90%	85%	80%	75%	70%
Height formula	21.0	11.3	5.4	2.2	0.8
Surface formula	20.1	10.5	4.8	1.8	0.6
Height-Weight formula	19.8	10.2	4.5	1.7	0.6

It will be seen that in the case of college students the fluctuations from a formula based on both height and weight are less than the fluctuations from a formula based on height alone. Between the formula based on the calculated body surface area, and the formula based on linear relationships between vital capacity and height and weight, there is no significant difference. This conclusion, of course, applies only to college students. The significance of these standard deviations can better be appreciated if one compares how many out of each hundred college students will have a vital capacity that falls below any assumed percentage of the calculated vital capacity. Table 3 gives these figures.

Of every hundred college students approximately twenty-one will have a vital capacity less than 90 per cent. of that calculated by the height formula, and approximately twenty will have a vital capacity less than 90 per cent. of that calculated by the body surface or by the height-weight formula. On the other hand, only about two will have a vital capacity less than 75 per cent. of the calculated amount. We

have compared the calculated fluctuations among Stanford students with those actually observed and find a close agreement between the two.

DISCUSSION

College students constitute an excellent group for determining normal vital capacity standards. They are young, intelligent and healthy. In this test intelligence is a factor because the test demands a maximum effort and statistics might easily be impaired if some subjects did not understand the instructions or did not make the necessary effort.

By applying statistical methods of study to the figures obtained from college students we have determined which gave the best index of vital capacity—the height, the weight or a combination of these; we have obtained formulas by which one may predict the average vital capacity for students from their heights or a combination of these with their weights; and we have defined the probable fluctuations from these calculated averages. Unfortunately, we have not the figures necessary for comparing the vital capacity with the sitting or with Dreyer's stem height, but we hope later to report on the value of this standard as judged by college statistics.

Most standards for vital capacity are based on the assumption that there is a simple ratio between the vital capacity and some body measurement or some power of this measurement. Thus the ratio to the height, to the surface area or to some power of the weight or stem length is given. Statistical formulas usually introduce an additional constant which is added to or subtracted from one side of the equation. This distinguishes our formulas from those that have been proposed.

Our formulas are strictly applicable only to college students. How far may they applied to a larger field? We have no figures which answer this question but it is evident from the work of others that they are quite inapplicable to females in general,[4] as well as boys.[8] Furthermore, our standard is a high one for men at large, partly because college students represent a picked class and, partly, because the vital capacity tends to lessen as persons grow older. Excess fat is a disturbing factor in any formula which is based on weight. For this reason we have given no weight formula and we suspect that for men in general a formula based on height and weight combined may be no better than one based on height alone.

Vital capacity varies considerably even in such a selected group as college students and even when it is compared with the height or with a combination of height and weight. The amount of these

8. Emerson, P. W., and Gue, H.: Vital Capacity of the Lungs of Children, Am. J. Dis. Child. **22**:202 (Aug.) 1921.

variations is shown in Table 3. What constitutes an abnormal reduction of the vital capacity? The answer to this question depends on whether we are comparing individuals or group averages with the standard. The difference between different groups of normal individuals is illustrated by the deviations of the Oxford average and the Harvard medical average from our standard for college students. Making allowances for height, the former is 2.5 per cent. below the average and the latter 8.7 per cent. above the average. To be significant, a group average should probably differ from the college standard by not less than 10 per cent. With respect to individual observations, our study shows that of every hundred college students about two have a vital capacity that is less than 75 per cent. of the standard. Assuming that an occasional student has some unrecognized disease, we may conclude that for men in general a reduction below 70 per cent. of the standard is almost always abnormal. Studies on heart patients and on patients with pulmonary tuberculosis indicate that in these diseases the vital capacity frequently falls below this figure.

CONCLUSIONS

1. Among college students the correlation of vital capacity with height and the correlation of vital capacity with weight are approximately equal. The correlation of vital capacity with a combination of weight and height is a little better than the correlation with either separately.

2. Formulas are given which express the average vital capacity of college students for different heights and combinations of height and weight.

3. From these formulas there is a very considerable fluctuation even among college students. The fluctuations for men in general, and the deviations in disease must necessarily be still greater.

THE LENGTH OF LIFE OF TRANSFUSED ERYTHROCYTES IN PATIENTS WITH PRIMARY AND SECONDARY ANEMIA *

JOSEPH T. WEARN, M.D.,
SYLVIA WARREN AND OLIVIA AMES
BOSTON

Introduction.—During recent years, and especially since the introduction of the sodium citrate method, blood transfusion has become one of the most common forms of treatment of the various types of primary and secondary anemias. Thus far, however, little is known as to the length of life of the transfused erythrocytes in patients with primary and secondary anemia, and until the recent work of Ashby [1] no observations had been made on this subject. This investigator studied the length of life of transfused red corpuscles in pernicious anemia and found the average to be about three months. Previous to this time various observers had claimed the length of life of the red corpuscles to be from fourteen to fifty-two days.[2] Information on this point seemed desirable in that it might demonstrate the practical value of transfusion, serve as an aid in deciding what the proper intervals between transfusions should be, and because of its relation to the debated problem as to whether or not there is an increase of hemolysins in the blood serum of individuals with primary and secondary anemias.

It is generally known that the transfusion of blood is a safe procedure when the donor's cells are compatible with the plasma of the recipient. The fact that the donor's plasma may agglutinate and hemolyze the cells of the recipient is negligible because the donor's plasma is diluted so rapidly as it enters the recipient's blood stream that agglutination and hemolysis are impossible. It follows then that Group IV blood (Moss classification) may be transfused without ill effects into persons whose bloods fall into Groups I, II and III. In a similar manner a recipient in Group I may be transfused with bloods of Groups II, III and IV.

---

* From the Medical Service of the Peter Bent Brigham Hospital.

* This paper is No. 20 of a series of studies on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed from a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1. Ashby: J. Exper. M. **29**:267, 1919.

2. Ashby: M. Clin N. America, November, 1919; J. Exper. M. **29**:267, 1919. Ward and Muller; Von Ott; Hunter, W.: Quoted by Ashby, J. Exper. M. **29**:207, 1919.

Technic.—Ashby has devised an ingenious method of following the life of the transfused red blood cells by means of group agglutination.[3] Blood is taken from the recipient's finger and mixed with citrated blood serum which will agglutinate the cells of the recipient but not the cells which have been transfused. The unagglutinated cells (i. e., those that have been transfused) may then be counted. The technic of the method is as follows (assuming a Group II recipient and a Group IV donor): The blood of the recipient is taken in a leukocyte counting pipet up to the 0.5 mark, and is diluted up to the 11 mark with the agglutinating fluid, which is made up of Group IV serum and a 4.4 per cent. solution of sodium citrate in the proportion of 1:20. The pipet is shaken and the mixture expelled into a small test tube in which it is incubated at 37 C. for forty minutes, with thorough shakings every ten minutes. It is then left in the icebox over night. Just before counting, the mixture is shaken and a drop placed in the blood counting chamber and, as directed by Ashby, "160 small squares in each of the two chambers are counted, the average of the counts taken and multiplied by 1100/2 to give the number of unagglutinated or transfused corpuscles per cubic millimeter of blood." Controls on the activity of the agglutinating serum are made by using the technic described above on blood of an untransfused individual in Group II. Theoretically, all the Group II cells should be agglutinated by the Group IV serum; practically, however, there remain unagglutinated on an average of from 20,000 to 50,000 cells per c.mm. Serum which will agglutinate the blood of a normal person in Group II, leaving only 50,000 cells per c.mm. unagglutinated may be considered to be active. When the unagglutinated cell counts in transfused individuals remain higher than these control counts, it may be assumed that the number of unagglutinated corpuscles in excess of the control count represent the number of unagglutinated donor's cells present in the circulation. Cases have been studied by us according to Ashby's method and technic. All counts have been made in duplicate, and the figures in the accompanying tables represent the average. In the cases reported, controls on the serum were made as described above, and, except in two instances, the same agglutinating serum was used throughout for all patients. Control counts of the new and old serums were shown to be practically identical before the changes were made.

Observations on Patients with Pernicious Anemia.—Four patients with pernicious anemia, whose bloods were in Group II, were transfused with citrated blood from donors in Group IV. Counts were then made of the transfused or unagglutinated cells in the bloods of these recipients, and repeated many times until the total transfused cells dropped to the level of the control counts. These patients presented the clear cut and classical signs and symptoms of primary

3. Ashby: J. Exper. M. **34**:147, 1921.

anemia, but among them were representatives of the different stages of the disease. Patient A was in the sixth year of the disease, was bedridden and had been observed in a remission during his stay in the hospital the year before, but in a series of counts taken before his transfusion his erythrocytes were found to be steadily decreasing. Patient C, in the third year of the disease, was also bedridden and his red blood cell counts showed the same general curve as the counts of Patient A. In contrast, Patients B and D were in the earlier stages of the disease, had been able to do some work and were ambulatory at the time of their transfusion.

The observations on Patient D are of especial interest in that the donor for transfusion was another patient with pernicious anemia (Group IV). When the donor was bled, 300 c.c. were withdrawn and he was immediately transfused with 800 c.c. of normal blood. The volume of cells in the 300 c.c. of pernicious anemia blood being very small, the unagglutinated cell count in this recipient never rose above 97,000 per c.mm. Frequent counts were made in this case, and the control counts which were made on untransfused normals in Group II and also on the blood of an untransfused patient with pernicious anemia in Group II, agreed closely.

REPORT OF CASES

CASE 1.—Patient A (Medical No. 13211) was a man, aged 41, belonging to Group II. His symptoms began four years before his entrance to the hospital. They were weakness, pallor, distress after eating and numbness of the fingers and toes. Two years previously, while under observation in the hospital, he had a typical remission with marked improvement of all his symptoms except the numbness of the extremities. Eight months later he again began to grow steadily weaker. In the month previous to his present entrance to the hospital his red cell count dropped from 1,332,000 to 676,000. He was then transfused with 575 c.c. citrated blood of Group IV. Blood findings before transfusion were: white cell count, 2,500 per c.mm.; hemoglobin, 30 per cent.; platelets, 98,000 per c.mm.; reticulated cells, 0.5 per cent. The blood picture was typical of pernicious anemia (Table 1, Fig. 1).

TABLE 1.—BLOOD PICTURE OF PATIENT A

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Nov. 16, 1920	1,152,000	
18	Dec. 3, 1920	Transfused 575 c.c. citrated blood, Group IV	
18	Dec. 3, 1920	1,024,000	530,000
23	Dec. 8, 1920	1,936,000	535,700
28	Dec. 13, 1920	1,800,000	691,900
49	Jan. 3, 1921	1,552,000	553,850
59	Jan. 13, 1921	1,216,000	464,200
56	Jan. 20, 1921	848,000	349,800
73	Jan. 27, 1921	1,344,000	300,300
77	Jan. 31, 1921	811,436	148,500
78	Feb. 1, 1921	884,268	238,250
79	Feb. 2, 1921	Transfused 600 c.c. citrated blood, Group II	
85	Feb. 8, 1921	1,160,000	229,900
91	Feb. 14, 1921	1,160,000	
95	Feb. 18, 1921	1,088,000	
101	Feb. 24, 1921	904,000	301,400
106	March 1, 1921	1,328,000	351,450
110	March 4, 1921	1,744,000	258,500
116	March 10, 1921	1,312,000	122,650
120	March 14, 1921	1,094,808	100,650
128	March 22, 1921	848,000	73,150

Case 2.—Patient B (Medical No. 15159), a woman aged 46, also belonged to Group II. Her illness began one year before admission to the hospital. The symptoms were gradually increasing weakness and pallor, several attacks of diarrhea and slight numbness of the fingers. She had been able to do a little work around the house. Her blood report before transfusion was as follows: Red cell count, 3,456,000 per c.mm.; reticulated cells, 0.9 per cent.; white cell count, 4,700 per c.mm.; platelets, 151,000 per c.mm. The blood smears showed the typical findings of pernicious anemia. She was transfused with 400 c.c. of citrated blood from a Group IV donor (Table 2, Fig. 2).

TABLE 2.—Blood Findings of Patient B

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Jan. 9, 1921	3,456,000	
1	Jan. 9, 1921	Transfused 400 c.c. citrated blood, Group IV	
3	Jan. 11, 1921	4,152,000	464,750
13	Jan. 21, 1921	4,648,000	381,150
19	Jan. 27, 1921	4,338,000	282,150
24	Feb. 1, 1921	4,256,000	247,500
31	Feb. 8, 1921	3,792,000	307,450
38	Feb. 15, 1921	5,446,000*	
51	Feb. 28, 1921	5,328,000	259,600
55	March 4, 1921	3,668,000	347,800
75	March 24, 1921	4,368,000	216,150
90	April 8, 1921	4,214,000	110,000
98	April 16, 1921	4,320,000	106,150
111	April 29, 1921	4,556,000	35,200

* The sudden rise in the total red blood cell curve was due to a short remission as shown by a sudden increase in the number of reticulated red cells just previous to the rise in the total red cell count.

Case 3.—Patient C (Medical No. 14705) was a woman, aged 55, belonging to Group II. Two years before entrance to the hospital, a gradually increasing weakness, pallor and gastric distress marked the onset of her illness. Then she developed numbness of the hands and feet. Her blood findings before transfusion were: hemoglobin, 45 per cent.; red cell count, 2,356,000 per c.mm.; reticulated cells, 1.5 per cent.; white cell count, 4,100 per c.mm. The stained smear was typical of pernicious anemia. She was transfused with 600 c.c. citrated blood from a Group IV donor and later had several transfusions of Group II blood (Table 3, Fig. 3).

TABLE 3.—Blood Findings of Patient C

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Jan. 18, 1921	1,268,000	
1	Jan. 18, 1921	Transfused 250 c.c. citrated blood, Group IV	
3	Jan. 21, 1921	1,028,000	238,150
7	Jan. 25, 1921	Transfused 600 c.c. citrated blood, Group II	
10	Jan. 28, 1921	2,356,000	165,000
14	Feb. 1, 1921	2,016,000	161,700
16	Feb. 3, 1921	Transfused 550 c.c. citrated blood, Group II	
17	Feb. 4, 1921	2,776,000	189,750
43	March 19, 1921	1,300,000	124,850
43	March 19, 1921	Transfused 500 c.c. citrated blood, Group II	
71	April 16, 1921	1,544,000	57,750

Case 4.—Patient D (Medical No. 15642), a man aged 50, belonging to Group II, noticed symptoms of weakness and pallor three months before admission to the hospital. One month later he had a sore tongue, distress after eating and numbness of the fingers. He had been able to work until shortly before he entered the hospital. His blood findings at entrance were as follows: hemoglobin, 18 per cent.; red cell count, 1,224,000 per c.mm.; reticulated cells, 0.9 per cent.; white cell count, 5,600 per c.mm., and platelets, 128,000 per c.mm. The smear was characteristic of pernicious anemia. He was transfused with 300 c.c. of Group IV blood from another patient who had a typical pernicious anemia (Table 4, Fig. 4).

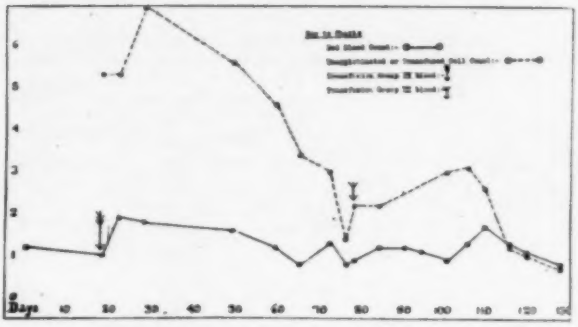


Fig. 1.—Blood findings of Patient A. In this and the accompanying charts the figures on the left border represent millions in the total red blood cell counts, and hundreds of thousands in the unagglutinated or transfused red blood cell counts.

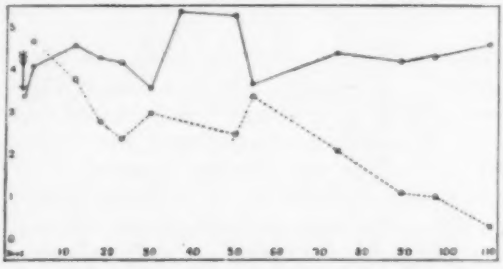


Fig. 2.—Blood findings of Patient B.

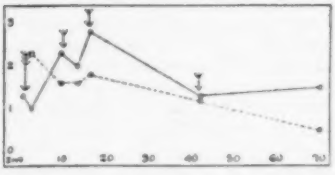


Fig. 3.—Blood findings of Patient C.

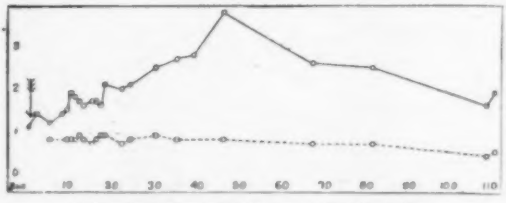


Fig. 4.—Blood findings of Patient D.

TABLE 4.—Blood Findings of Patient D

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	March 19, 1921	1,224,000	
1	March 19, 1921	Transfused 300 c.c. citrated blood, Group IV (P. A.)	
3	March 22, 1921	1,401,000	
6	March 25, 1921	1,200,000	86,350
9	March 28, 1921	1,448,000	
10	March 29, 1921	1,520,000	89,650
11	March 30, 1921	1,928,000	87,100
12	March 31, 1921	1,864,000	86,900
13	April 1, 1921	1,704,000	94,600
14	April 2, 1921	1,648,000	80,850
16	April 4, 1921	1,680,000	78,650
17	April 5, 1921	1,688,000	84,150
18	April 6, 1921	1,568,000	94,050
19	April 7, 1921	2,144,000	90,200
23	April 11, 1921	2,064,000	78,100
25	April 13, 1921	2,120,000	80,850
31	April 19, 1921	2,560,000	96,800
36	April 24, 1921	2,688,000	84,700
40	April 28, 1921	2,804,000	
47	May 5, 1921	3,832,000	82,500
68	May 26, 1921	2,600,000	75,900
82	June 9, 1921	2,528,000	74,250
100	July 6, 1921	1,600,000	47,850
111	July 8, 1921	1,872,000	54,833

Observations on Patients with Secondary Anemia.—Four cases (E, F, G and H) of secondary anemia, accompanying an advanced nephritis, were studied in the same way. Before transfusion, the patients showed progressive anemias as proved by decreasing red cell counts. Patients F and H were bleeding constantly from the kidneys and their urines showed gross blood. Patient E had a very small amount of blood in the urine, averaging from five to six red blood corpuscles per low power field when examined microscopically, while Patient G showed no evidence of hematuria or bleeding elsewhere.

Case 5.—Patient E (Medical No. 15126), a man, aged 32, in Group II, had had chronic nephritis for about six months before admission to the hospital. On entry his systolic blood pressure was 190; diastolic, 110. Phenolsulphonephthalein excretion was 42 per cent., blood urea nitrogen, 20 mg. per hundred c.c. of blood. His urine showed a few red blood cells constantly, averaging about five or six per low power microscopic field. The blood findings were: hemoglobin, 60 per cent.; red cell count, 4,060,000 per c.mm.; reticulated cells, 0.9 per cent.; white cell count, 9,650 per c.mm. The red corpuscles were practically normal in size and shape but showed definite achromia. He was transfused with 600 c.c. citrated blood from a Group IV donor (Table 5, Fig. 5).

TABLE 5.—Blood Findings of Patient E

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Jan. 15, 1921	4,060,000	
1	Jan. 15, 1921	Transfused 600 c.c. citrated blood, Group IV	
4	Jan. 18, 1921	4,644,000	623,700
42	March 1, 1921	4,992,000	244,750
52	March 11, 1921	4,792,000	332,750
64	March 23, 1921	4,560,000	239,800
70	March 29, 1921	4,656,000	162,250
77	April 5, 1921	4,008,000	143,550
84	April 12, 1921	3,544,000	90,750
92	April 20, 1921	3,368,000	94,600
99	April 27, 1921	3,420,000	82,650
108	May 6, 1921	2,986,000	151,800
119	May 17, 1921	3,248,000	34,650

Case 6.—Patient F (Medical No. 15371), a man, aged 23, in Group II, had had influenza followed by acute nephritis two years before his entrance to the hospital. He has passed bloody urine constantly since that time and throughout his stay in the hospital the urine showed gross blood. The phenolsulphonephthalein excretion varied from 18 to 35 per cent.; blood urea nitrogen was from 26 to 61 mg. per hundred c.c. on a low protein diet. Blood findings before transfusion were as follows: hemoglobin, 65 per cent.; red cell count, 4,512,000 per c.mm.; reticulated cells, 2 per cent.; white cell count, 11,200 per c.mm. The smear showed slight achromia of the red cells but was otherwise essentially normal in appearance. He was transfused with 550 c.c. citrated blood from a Group IV donor (Table 6; Fig. 6).

TABLE 6.—Blood Findings of Patient F

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	March 28, 1921	4,572,000	
9	April 5, 1921	Transfused 550 c.c. citrated blood, Group IV	
10	April 6, 1921	3,664,000	248,050
12	April 8, 1921	3,974,000	275,550
15	April 11, 1921	4,040,000	259,600
17	April 13, 1921	4,160,000	296,450
23	April 19, 1921	4,736,000	294,800
30	April 26, 1921	3,072,000	208,450
36	May 2, 1921	3,216,000	202,950
39	May 5, 1921	3,552,000	242,000
46	May 12, 1921	3,416,000	189,200
53	May 19, 1921	3,208,000	143,000
56	May 22, 1921	4,288,000	176,550
69	June 4, 1921	2,816,000	156,750
92	June 27, 1921	3,828,000	83,600
96	July 1, 1921	3,600,000	68,750
108	July 13, 1921	3,506,448	42,185
114	July 19, 1921	4,016,000	33,000

Case 7.—Patient G (Medical No. 14976), a man, aged 33, in Group II, had had nephritis for about eight months. Physical examination revealed ascites and considerable edema of the genitals and lower extremities. The blood pressure was: systolic, 128; diastolic, 96. Phenolsulphonephthalein excretion was 13 per cent., and blood urea nitrogen was 25 mg. per hundred c.c. The urinary sediment contained many hyalin, granular and waxy casts but no red blood cells. Before transfusion the red count was 3,736,000 per c.mm.; reticulated cells, 0.9 per cent.; hemoglobin, 45 per cent. The stained smear showed practically normal red cells with slight achromia. He was transfused with 250 c.c. citrated blood (containing 10,000,000 red corpuscles per c.mm.) from a donor in Group IV (Table 7, Fig. 7).

TABLE 7.—Blood Findings of Patient G

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	March 28, 1921	3,764,000	
35	May 2, 1921	2,896,000	
45	May 22, 1921	3,736,000	45,650
57	May 24, 1921	Transfused 250 c.c. citrated blood, Group IV	
59	May 26, 1921	5,064,000	253,000
67	June 3, 1921	4,576,000	261,250
74	June 10, 1921	3,984,000	309,850
79	June 15, 1921	4,688,000	280,500
85	June 21, 1921	5,024,000	265,650
94	June 30, 1921	4,416,000	163,350
105	July 11, 1921	4,344,000	179,300
112	July 18, 1921	3,712,000	130,550
142	August 17, 1921	4,456,000	69,300
150	August 25, 1921	4,128,000	86,100
156	August 31, 1921	4,800,000	49,550

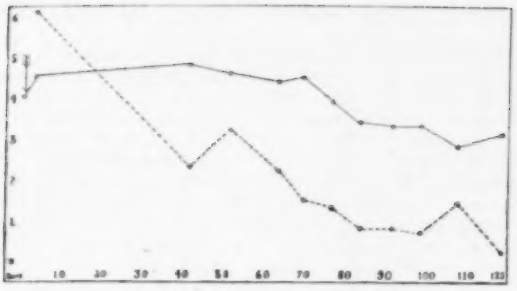


Fig. 5.—Blood findings of Patient E.

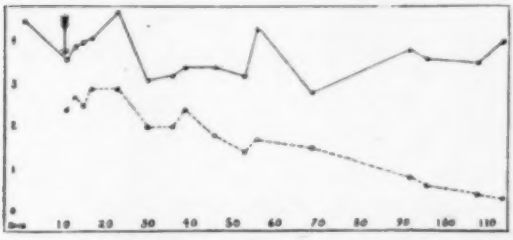


Fig. 6.—Blood findings of Patient F.

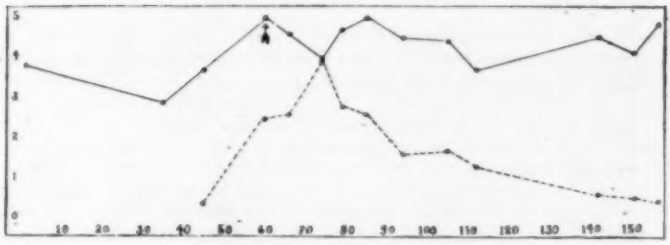


Fig. 7.—Blood findings of Patient G.

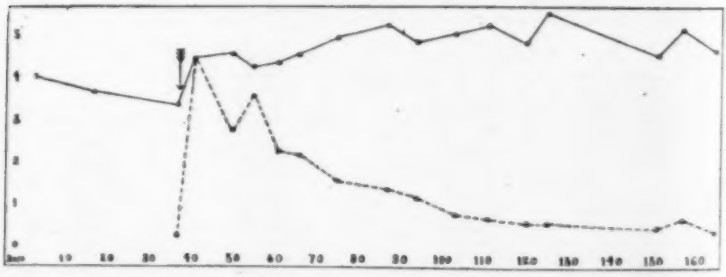


Fig. 8.—Blood findings of Patient H.

CASE 8.—Patient H (Medical No. 15653), a boy, aged 16, in Group II had nephritis, of two months' duration, which followed a respiratory infection. He was not edematous and his blood pressure was: systolic, 148; diastolic, 90. The urinary sediment contained hyalin and finely granular brown casts and many red blood cells so that the blood was visible grossly from time to time. Phenolsulphonephthalein excretion was 50 per cent., and the blood urea nitrogen was 12 mg. per hundred c.c. His red cell count before transfusion was 3,360,000 per c.mm.; reticulated cells, 2.2 per cent.; hemoglobin, 52 per cent.; white cell count, 6,900 per c.mm. The stained smear showed slight achromia of the red corpuscles. He was transfused with 250 c.c. citrated blood (containing 10,000,000 red corpuscles per c.mm.) from a Group IV donor (Table 8, Fig. 8).

TABLE 8.—BLOOD FINDINGS OF PATIENT H

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	April 16, 1921	4,144,000	
17	May 2, 1921	3,672,000	
37	May 22, 1921	3,360,000	
39	May 24, 1921	Transfused 250 c.c. citrated blood, Group IV	
41	May 26, 1921	4,497,000	451,550
49	June 3, 1921	4,560,000	281,130
56	June 10, 1921	4,344,000	306,350
61	June 15, 1921	4,408,000	238,150
66	June 20, 1921	4,456,000	226,000
75	June 29, 1921	5,000,000	162,250
87	July 11, 1921	5,256,000	141,350
94	July 18, 1921	4,904,000	123,750
103	July 27, 1921	5,144,000	88,000
111	August 4, 1921	5,344,000	79,750
119	August 12, 1921	4,992,000	62,700
124	August 17, 1921	5,616,000	68,200
150	August 25, 1921	4,592,000	58,850
156	August 31, 1921	5,208,000	78,100
164	Sept. 8, 1921	4,688,000	48,960

DISCUSSION

Unfortunately it has not been possible in this investigation to study the length of life of cells transfused into normal individuals, but, in the light of the present findings, further studies on normals should be made. Ashby observed only one normal case until the transfused corpuscles disappeared from the circulation and found that they lived for thirty-nine days, while in her other two cases, which were followed incompletely, the cells lived about thirty-two days. In a later study, this author reports the length of life of transfused red blood cells in eight patients "without blood disease" to be very variable, some living as long as one hundred days, others disappearing in thirty days. The protocols of these patients, however, show that some of them had cancer or other malignant growths, one was in the tertiary stage of syphilis and none can be regarded as normal. Indeed, one finds included in the list patients with some of the most common and frequent causes of secondary anemia, and while in the technical sense of the term they may be "without blood disease" they show a decided disturbance of the blood.

Ashby found the length of life of the transfused erythrocytes in pernicious anemia to be about three months and concluded that there was no hemolytic toxin producing the anemia in this disease. The

results of this investigation show the length of life of the transfused corpuscles in primary anemia, and in the one type of secondary anemia studied, to be from seventy-one to one hundred and ten days, but it is felt that no conclusion regarding the presence of a hemolysin is justifiable, because these observations furnish no direct evidence on this point, and also because of the lack of accurate information as to the duration of life of red corpuscles transfused into normal persons. Furthermore, no evidence could be found to support the claim, made by Ashby, that "on the whole, blood destruction is quiescent in pernicious anemia." The results here show merely that the length of life of transfused erythrocytes is greater in patients with primary anemia and with secondary anemia due to nephritis, than in the one normal case on record; and this is only known to be true when the donor and recipient are of unlike groups. Whether or not the same would hold true when the donor and the recipient are in the same group it is not possible to say. In addition, these observations do not throw any light on what is happening to the patient's own cells during this period, and there is no reason to believe that the rate of destruction of the transfused cells is any indication of the rate of destruction of the patient's own cells, for it is possible that the transfused erythrocytes, belonging to a group foreign to the patient, are not acted on in the same manner as the patient's own cells.

It has not been proved conclusively that the transfused blood cells function during their stay in the circulation, but the fact that many of the patients show some clinical improvement after transfusion suggets that this is the case. Moreover, the observations of several investigators have shown that any foreign material, such as manganese or carbon particles and foreign blood cells, when injected into the blood stream of an animal are removed quickly.[4] This being the case, if the transfused cells were not living and functioning as normal red blood corpuscles one would expect them to be removed from the blood stream.

Several rises in the counts of transfused red cells were noted just before their final disappearance (Figs. 1 and 5). As the control counts on these days did not increase, and there was no variation in technic, differential counts of the number of microcytes were made to see if a breaking up or fragmentation of cells might account for these rises, but no evidence to support this theory was found. In view of the coincident rise of the total red blood cell count, it is not unlikely that changes in the blood volume account for the rise. One other possible explanation of this occurrence is that following transfusion there may be a definite improvement in the circulation with a resulting rise in

4. McJunkin: J. Exper. M. **21**:59, 1918. Lund, Shaw and Drinker: J. Exper. M. **33**:231, 1921. Drinker and Shaw: J. Exper. M. **33**:77, 1921.

the number of circulating cells in the periphery. This seems plausible in Case. 1.

The most striking result of these observations on the life of the transfused cells in the primary and secondary anemias is their surprisingly long stay in the circulation of the recipient. The longest period before the disappearance of the last cells was 113 days and the shortest fifty-nine days, the average for all these observed being about eighty-three days. It must be remembered that in addition to this period of life as transfused erythrocytes in a foreign circulation, that some of these corpuscles were functioning as adult cells in the donor before they were transferred, but of the length of time that they had been in the adult stage nothing is known, nor is there any accurate knowledge of the period of time required for a red blood cell to pass from its immature nucleated stage to its adult nonnucleated stage. These considerations, together with the findings of this investigation, indicate that the life of the human red blood cell is much longer than has been believed to be the case. Whether the duration of life and the stages of development of these cells would have been the same in the circulation of the individual from whom they originally came it is not possible to say.

It is also of interest that the life of the transfused red cells in both secondary and primary anemias was of the same duration. It seems almost probable that the transfused cells are adult red corpuscles of varying ages, and this, if true, would account for their steady gradual disappearance from the circulation of the recipient, also for the fact that some of the cells begin to disappear almost immediately after transfusion. This explanation is also compatible with the idea that new red corpuscles are being constantly supplied to the circulation. There were no sudden drops in the transfused cell count during these observations, but this may be due to the time intervals between counts, and in this connection it will be noted that two of the patients with pernicious anemia were women, both of whom had ceased to menstruate, so that no loss of transfused cells can be accounted for by that route, as noted by Ashby. In Case 6, in which there was constantly a large amount of blood in the urine, an attempt was made to determine the number of transfused corpuscles that were being lost in this way, but this was unsuccessful as the total unagglutinated count of the red corpuscles in the urine after centrifugalization was less than the control counts of the agglutinating serum on normal Group II blood.

Another point that is clearly brought out in this study is that due to the long life of the transfused red cells one may expect to tide patients over the acute stages of primary and secondary anemias by purely mechanical means. The improvement after some transfusions,

except when a real remission begins, might be explained by the increase in oxygen carriers. This improvement, which is generally of about two or three months' duration, is probably governed by the fact that some of the transfused corpuscles seem to function between sixty and ninety days.

CONCLUSIONS

Red blood corpuscles from donors in Group IV transfused into patients in Group II with pernicious anemia and anemia secondary to nephritis, remained in the circulation longer than has been generally believed to be the case. The last of the transfused red blood cells disappeared from the circulation in from fifty-nine to 113 days, with an average of eighty-three days.

No difference was noted in a series of observations in the duration of the stay of the transfused red blood corpuscles in the circulation between patients with primary anemia and secondary anemia (due to nephritis).

In a single observation red blood corpuscles from a patient with pernicious anemia transfused into another patient with pernicious anemia, behaved as did the corpuscles from normal donors.

BLOOD PRESSURE AND PULSE RATE LEVELS

FIRST PAPER: THE LEVELS UNDER BASAL AND DAYTIME CONDITIONS*

T. ADDIS
SAN FRANCISCO

This study is primarily concerned with the question of normal blood pressures and pulse rates under varying conditions. The observations on patients cover only a restricted field and are introduced, in the main, as illustrations of the deductions which may be drawn from comparison with the normal data. The work falls naturally into two parts, one, the measurement of the level of pressure and pulse rate under fixed conditions, with which this paper is concerned; the other, the measurement and interpretation of the changes in pressure and pulse rate induced by alteration of the conditions, which are dealt with in a succeeding paper. Most of the observations were made on soldiers at Camp Lewis, Wash. For the opportunity to do this work I am indebted to Dr. Kerr, who was in charge of the medical division of the Base Hospital, to Dr. Northington and Dr. Fulton who were successively in command, and to Lieutenant-Colonel Gibner who was camp surgeon.

The level of pressure and pulse rate under what we have called "basal" and "daytime" conditions is the subject of this paper. In work on metabolism the word basal is used to indicate that the measurements have been made in the early morning before food has been taken and before the subject has done any muscular work. In this paper it has the same significance. The observations were made in the early morning before the subjects had risen from bed. In most cases they were first awakened by the application of the arm band. By daytime observations are meant those taken at various times during the day after the subjects had risen from bed and had taken food. In all cases the readings were made while the men were lying down. Those who had recently done any strenuous muscular work were excluded. Most of the work was done on Sundays when bad weather had kept the men relatively inactive in their barracks.

The incentive to collect data on the normal basal blood pressure and pulse rate was derived from a difficulty in diagnosis in a group of patients who presented signs and symptoms resembling those seen in hyperthyroidism. While recruits from the first and second drafts were arriving at Camp Lewis, men were seen every day who combined an enlargement of the thyroid gland with tachycardia, tremor and evident

*From the Medical Department of Stanford University Medical School.

signs of nervous instability. It was recognized from the first that only a small percentage were likely to have exophthalmic goiter for true exophthalmos was rare. The hyperthyroidism which arises in some cases of endemic goiter is uncommon at the age period of the men we were examining, and we were dealing with a condition which was not at all uncommon. It was noted also that similar signs and symptoms were found in men who had no thyroid enlargement, and on this account a statistical study was made of the incidence of tachycardia, tremor and various other abnormalities in large groups of men with and without increase in the size of the thyroid gland.[1] This survey showed that there was no definite relationship between the thyroid enlargement and the occurrence of tachycardia, tremor and other evidences of vascular and nervous instability. It appeared, then, that the thyroid enlargement was only a chance concomitant which was frequently present simply because endemic goiter was so extremely prevalent in many of the districts from which the recruits were drawn.[2] It thus seemed still more unlikely that hyperthyroidism could be a frequent cause of the condition. We felt confident that the great majority of these men were suffering from the condition described under the names irritable heart, neurocirculatory asthenia and effort syndrome. But in individual cases there was often uncertainty, and this led to a search for some objective clinical evidence of an increase in basal metabolism, to take the place of the direct measurements of oxygen consumption which we could not at that time obtain.

A relationship has been shown to exist between the pulse rate and the metabolism when they are measured under the same conditions, and for some time we placed a great deal of weight on the pulse rate counted in the early morning before the patients had risen from bed. When the pulse rate was less than 70 in patients who during the day had tachycardia and tremor, we felt that we could probably exclude hyperthyroidism. However, the relation between pulse rate and rate of metabolism is not always close. It seems likely that the reason for the relation which does exist is to be found in a more general relation between the metabolic activity of the body as a whole and the activity of the circulatory system of which the pulse rate is only a partial expression. The true measure of circulatory activity is the volume flow of blood per unit of time. It has been shown by combined circulatory and metabolic measurements that there is a close correspondence between volume flow of blood and rate of metabolism. The volume flow of blood per unit of time has been determined in man by

1. Addis and Kerr: Arch. Int. Med. **23**:316 (March) 1919.
2. Kerr: Arch. Int. Med. **24**:347 (Sept.) 1919.

Lindhard [3] and by Means and Newburgh.[4] The output of the heart was measured by gas analysis methods over a short space of time during which the pulse rate was counted. The average output at each beat of the heart was thus calculated, and the volume flow of blood per minute obtained from the product of the systolic output per beat and the pulse rate per minute. In subjects on whom measurements were made before and after exercise a remarkably close agreement was found between the increase in this product and the increase in the rate of metabolism produced by exercise. Bainbridge [5] recently pointed out that a comparison of such experiments shows that the two factors in the product which measures the volume flow of blood—the systolic output per beat and the pulse rate—may each vary, although for given metabolic conditions the product will remain constant. The required volume flow of blood may at one time be obtained mainly by increase in systolic output and at another time mainly by increasing the pulse rate. This circumstance seems to account for the absence of any very direct relation between pulse rate and rate of metabolism, and it also indicates that if we were able to get some clinical measure of the systolic output at each beat of the heart, even though it were only approximate, we might have a better index of the rate of metabolism than can be obtained from the pulse rate alone.

Measurements of systolic output by the nitrous oxid or any other blood analysis method are usually out of the question in clinical work. But von Recklinghausen [6] has shown that the pulse pressure varies directly with the systolic output per beat, except for such variations as may arise from differences in the coefficient of elasticity in the arteries. This has recently been experimentally confirmed by Bazett.[7] It appeared, therefore, that the product of the pulse pressure and the pulse rate might have a close relation to the rate of metabolism unless differences in the elasticity of the arteries in different individuals were so marked as seriously to distort the relation between systolic output and pulse pressure. Even if that should be the case the P. P. (pulse pressure) $\times$ P. R. (pulse rate) product might still be a useful clinical method for the purpose of obtaining an indication of the direction of metabolic changes in the same individual at different times.

These considerations, but especially the results of experiments on the effect of exercise on the P. P. $\times$ P. R. product which are given in the next paper, made it seem worth while to collect data on

3. Lindhard: Arch. f. d. ges. Physiol. **161**:233, 1915.
4. Means and Newburgh: J. Pharmacol. & Exper. Therap. **7**:441, 1915.
5. Bainbridge: Physiology of Muscular Exercise, 1919.
6. Von Recklinghausen: Arch. f. exper. Path. **56**:1, 1907.
7. Bazett: Proc. Roy. Soc. London, Ser. B **90**:415, 1917.

the P. P. × P. R. product in normal persons under basal conditions in order to get a control for similar observations on patients. The results, of course, do not allow of any conclusion as to whether the P. P. × P. R. product has a closer or even as close a relation to the basal metabolic rate as the pulse rate alone. That question can only by answered by direct comparison with a parallel series of determinations of basal metabolism. But the figures have an interest of their own apart from any possible significance they may have in connection with basal metabolism. In addition to these early morning observations, the pressure and pulse rate was measured on another group of normal individuals during the day under the conditions we have defined above for daytime observations.

In both the basal and daytime observations the pressure and pulse rate were observed simultaneously, the pulse rate being counted by an assistant while the systolic and diastolic pressures were being read. A mercury sphygmomanometer with a broad arm band was used. The diastolic pressure was taken at the end of the third phase or at the cessation of sound in those subjects in whom no fourth phase could be distinguished.

In Table 1 the basal and daytime results on normals are compared. The basal averages were obtained from eighty-nine observations on seventy-six persons, and the daytime figures from 300 measurements on 300 persons. Both groups comprised soldiers on active service between the ages of 21 and 31.

These results are a contribution toward the accumulation of data required for a definition of what is meant by normal pressure and pulse rate. Though a great deal of work has been done on the subject, the figures have usually been presented in such a way as to preclude the application of the statistical methods which are essential for an adequate understanding of their significance. The variability of the systolic, diastolic and pulse pressure has been admirably dealt with by Kilgore,[8] and Alvarez and his associates [9] have published a complete statistical review of a large series of measurements of systolic pressure in normal individuals. Alvarez arranged his data in groups according to the ages of the subjects, but no significant change in the systolic pressure was found between the ages of 21 and 31. We may, therefore, compare his average systolic pressure of 126.5 on 2,930 men with our average of 127.4 on 300 men, and his coefficient of variation of 12 per cent. with ours of 13 per cent. So far as the diastolic and pulse pressure are concerned, the only data available for the determination

8. Kilgore: Lancet **2**:236, 1918.
9. Alvarez, Wulzen, Taylor and Starkweather: Arch. Int. Med. **26**:381 (Sept.) 1920.

of variability seem to be the frequency distributions of Barach and Marks [10] and of Kilgore.[8] All these results were obtained under conditions similar to those we observed in our daytime observations. Only a few isolated measurements were found which were carried out under what we have called basal conditions.

TABLE 1.—NORMAL DATA. BASAL MEASUREMENTS OF SEVENTY-SIX NORMALS COMPARED WITH DAYTIME MEASUREMENTS ON THREE HUNDRED NORMALS

Averages

	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	99	71	28	63	1764
Day	127	78	50	80	3980

Standard Deviations

	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	±11.0	± 9.7	± 8.5	± 8.1	± 635
Day	±17.0	±11.1	±13.8	±12.4	±1550

Coefficients of Variation

	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	11%	14%	30%	13%	36%
Day	13%	14%	28%	16%	39%

Frequency Distributions

Systolic			Diastolic			Pulse Pressure			Pulse Rate			P. P. × P. R		
Cl. Int.	Basal	Day	Cl. Int.	Basal	Day	Cl. Int.	Basal	Day	Cl. Int.	Basal	Day	Cl. Int.	Basal	Day
71- 80	9%	—	41- 50	5%	2%	11-20	27%	1%	37- 44	1%	—	0- 999	11%	—
81- 90	16%	2%	51- 60	51%	6%	21-30	45%	9%	45- 52	12%	—	1000- 1999	61%	6%
91-100	34%	6%	61- 70	39%	28%	31-40	25%	23%	53- 60	40%	5%	2000- 2999	26%	18%
101-110	34%	11%	71- 80	39%	34%	41-50	2%	33%	61- 68	30%	13%	3000- 3999	2%	31%
111-120	5%	22%	81- 90	6%	23%	51-60	1%	20%	69- 76	10%	27%	4000- 4999	..	19%
121-130	2%	28%	91-100	—	5%	61-70	—	7%	77- 84	3%	26%	5000- 5999	..	10%
131-140	—	10%	101-110	—	3%	71-80	—	4%	85- 92	2%	14%	6000- 6999	..	4%
141-150	—	10%	.....	.....	.....	81-90	—	3%	93-100	—	11%	7000- 7999	..	4%
151-160	—	4%	.....	.....	.....	.....	.....	.....	101-108	—	3%	8000- 8999	..	2%
161-170	—	1%	.....	.....	.....	.....	.....	.....	109-116	—	0.6%	9000- 9999	..	0%
171-180	—	1%	.....	.....	.....	.....	.....	.....	117-124	—	0.6%	10000-10999	..	0%
									125-132	—	0.3%	11000-11999	..	0.3%

The differences between the basal and day averages show how markedly the level of pressure and pulse rate is influenced by factors associated with daytime activities. A measure which would be "normal" for the day would be unusually high if it were found under basal conditions in the early morning, so that the interpretation of the significance of any given pressure or pulse rate depends, in the first place, on a knowledge of the conditions under which the observation was made.

During the day the P. P. × P. R. product increases more markedly than the other measurements because both pulse pressure and pulse rate rise. The increase in pulse pressure occurs in spite of a slight

10. Barach and Marks: Arch. Int. Med. **13**:648 (June) 1914.

increase in diastolic pressure and is due entirely to the rise in systolic pressure. Since the systolic pressure, other things being equal, is determined by the amount of blood pumped out by the heart, we may assume that during the day the output of the heart at each systole is increased. The increase in pulse rate shows that there are a larger number of systoles per unit of time. The changes induced by daytime conditions are, therefore, such as we should expect to find if there were an increase in the volume flow of blood.

There are two factors which are certainly of importance in raising the daytime levels. One of them is the effect of food, which has been shown by Weysse and Lutz [11] to result in an increase in systolic pressure and pulse rate. The other factor is exercise. In Table 2 averages are given from a group of ten normal persons under basal and daytime conditions and after a shorter or longer period of exercise.

TABLE 2.—Effect of Exercise on Blood Pressure and Pulse Rate Levels of Normal Individuals

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	100	65	35	60	2100
Day time	121	77	44	74	3256
Short exercise	137	59	78	81	6320
Longer exercise	168	42	126	114	14360

There is another factor—excitement—which may have been equally operative under both basal and daytime conditions. In Table 3 daytime averages from a group of twenty-seven men who were not excited are compared with averages from a group of twenty-seven men who admitted that the examination excited them because they were afraid that something would be found which would prevent them going over with their regiment.

TABLE 3.—Effect of Excitement on the Daytime Levels of Pressure and Pulse Rate in Normal Individuals

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
No excitement	122	79	43	80	3440
Excitement	154	89	65	92	5980

These three factors, food, exercise and excitement, all have their most marked effect on the systolic pressure and pulse rate. The measurement which is least influenced is the diastolic pressure. Food has little or no effect; exercise lowers it, and excitement increases it, but it remains the most stable measure, so that in daytime observations on patients when all three factors are operative, an increase in diastolic

11. Weysse and Lutz: Am. J. Physiol. **37**:330. 1915.

pressure is likely to be of more significance than the same degree of increase in systolic pressure.

The significance of any measurement which deviates from the normal average depends on the variability or degree of dispersion of the normal measurements. This variability is given in the standard deviation. The relation between the actual deviation of the measurement and the standard deviation can be expressed in a concrete way as odds against the possibility that any normal subject would give as high or a higher level of pressure or pulse rate than the measurement in question. A discussion of this statistical method will be found in a recent very complete study of blood pressure and pulse rate in children by Faber and James.[12] In Tables 4 and 5 the odds for a series of measurements for basal and daytime conditions are given.

TABLE 4.—BASAL CONDITIONS. THE ODDS THAT A NORMAL INDIVIDUAL UNDER BASAL CONDITIONS WILL SHOW AS HIGH OR A HIGHER LEVEL OF PRESSURE AND PULSE RATE AS THOSE GIVEN BELOW

Systolic	Odds	Diastolic	Odds	Pulse Pressure	Odds	Pulse Rate	Odds	P. P. × P. R.	Odds
118	1 in 24	88	1 in 25	43	1 in 26	77	1 in 24	2900	1 in 27
119	1 in 29	89	1 in 32	44	1 in 33	78	1 in 31	2950	1 in 33
120	1 in 36	90	1 in 40	45	1 in 44	79	1 in 42	3000	1 in 39
121	1 in 44	91	1 in 51	46	1 in 59	80	1 in 56	3050	1 in 47
122	1 in 55	92	1 in 67	47	1 in 80	81	1 in 76	3100	1 in 58
123	1 in 69	93	1 in 86	48	1 in 106	82	1 in 106	3150	1 in 69
124	1 in 86	94	1 in 112	49	1 in 147	83	1 in 147	3200	1 in 84
125	1 in 104	95	1 in 147	50	1 in 208	84	1 in 208	3250	1 in 104
126	1 in 141	96	1 in 204	51	1 in 306	85	1 in 308	3300	1 in 128
127	1 in 182	97	1 in 270	52	1 in 417	86	1 in 435	3350	1 in 161
128	1 in 233	98	1 in 385	53	1 in 625	87	1 in 666	3400	1 in 201
129	1 in 313	99	1 in 526	54	1 in 910	88	1 in 1000	3450	1 in 256
130	1 in 417	100	1 in 770	55	1 in 1430	.....	.....	3500	1 in 323
131	1 in 555	101	1 in 1000	.....	.....	.....	.....	3550	1 in 417
132	1 in 741	.....	.....	.....	.....	.....	.....	3600	1 in 526
133	1 in 1000	.....	.....	.....	.....	.....	.....	3650	1 in 666
								3700	1 in 833
								3750	1 in 1111

The odds given in these tables refer only to the normal, they cannot be interpreted as odds in favor of abnormality. To know the latter, we should have to measure the standard deviation of the group of abnormals to which the patient happened to belong. However, for practical purposes of classification of cases it is permissible arbitrarily to decide that any patient whose pressure exceeds a certain level shall be regarded as "abnormal." The choice of that level will depend on the nature of the work. It is sometimes desirable to have a standard so narrow that all cases with a possible pathologic tendency to hypertension will be detected. Then a level at which the odds are that only one normal out of, say, twenty-five would give as high a pressure may be taken. But at other times one may desire to separate a group of

12. Faber and James: Am. J. Dis. Child. **22**:7 (July) 1921.

cases in which it is practically certain that there are no normals. Then a level at which the chances are that only one out of 1,000 normals will be so high may be selected as the dividing point.

These statistical methods give no information as to the nature of the factor responsible for any unusually high pressure which may be found in a patient. If it is a daytime observation it may be the result of an abnormal susceptibility to purely external and evanescent causes such as food, excitement or exercise, rather than the inner and more lasting perversion of function we are accustomed to think of in connection with hypertension.

TABLE 5.—Daytime Conditions. The Odds That a Normal Individual Under Daytime Conditions Will Show as High or a Higher Level of Pressure or Pulse Rate as Those Given Below

Systolic	Odds	Diastolic	Odds	Pulse Pressure	Odds	Pulse Rate	Odds	P. P. × P. R.	Odds
160	1 in 22	97	1 in 23	74	1 in 24	102	1 in 27	6700	1 in 26
161	1 in 26	98	1 in 29	75	1 in 29	103	1 in 32	6800	1 in 29
162	1 in 29	99	1 in 34	76	1 in 33	104	1 in 38	6900	1 in 33
163	1 in 33	100	1 in 42	77	1 in 40	105	1 in 47	7000	1 in 39
164	1 in 38	101	1 in 52	78	1 in 47	106	1 in 55	7100	1 in 45
165	1 in 44	102	1 in 65	79	1 in 56	107	1 in 69	7200	1 in 53
166	1 in 51	103	1 in 82	80	1 in 67	108	1 in 84	7300	1 in 62
167	1 in 58	104	1 in 104	81	1 in 80	109	1 in 101	7400	1 in 74
168	1 in 69	105	1 in 133	82	1 in 98	110	1 in 128	7500	1 in 86
169	1 in 78	106	1 in 170	83	1 in 119	111	1 in 161	7600	1 in 104
170	1 in 91	107	1 in 222	84	1 in 145	112	1 in 204	7700	1 in 122
171	1 in 106	108	1 in 286	85	1 in 182	113	1 in 250	7800	1 in 147
172	1 in 125	109	1 in 385	86	1 in 222	114	1 in 323	7900	1 in 175
173	1 in 147	110	1 in 500	87	1 in 270	115	1 in 416	8000	1 in 208
174	1 in 175	111	1 in 666	88	1 in 333	116	1 in 526	8100	1 in 256
175	1 in 207	112	1 in 910	89	1 in 417	117	1 in 714	8200	1 in 303
176	1 in 250	113	1 in 1250	90	1 in 526	118	1 in 910	8300	1 in 385
177	1 in 294	.....	.....	91	1 in 666	119	1 in 1250	8400	1 in 455
178	1 in 345	.....	.....	92	1 in 884	.....	.....	8500	1 in 588
179	1 in 417	.....	.....	93	1 in 1111	.....	.....	8600	1 in 714
180	1 in 500	.....	.....	.....	.....	.....	.....	8700	1 in 833
181	1 in 625	.....	.....	.....	.....	.....	.....	8800	1 in 1111
182	1 in 740								
183	1 in 909								
184	1 in 1111								

The striking difference between the averages of normal individuals under basal and daytime conditions are the clearest illustration of the necessity for uniformity in the conditions under which the observations are made. It is not possible to use the basal normal for the evaluation of pressures obtained in patients in the morning if they have been out of bed even for a moment. The normal values for daytime measurements cannot be taken as a standard for observations made on patients who are standing or sitting, or on those who have just walked up a flight of stars. The variability of normal blood pressure under such conditions is not known.

1. IRRITABLE HEART

The measurements on patients were carried out under the same basal conditions as were observed with the normal controls. The cases

were in each instance tentatively diagnosed as cases of irritable heart with the exception that a reservation was made in regard to the possibility of true hyperthyroidism. These cases were selected from a larger group on the following basis. The patients all complained of one or more of three cardiac symptoms—dyspnea, palpitation, precordial pain; one or more of the three symptoms of vascular instability—dizziness, flushing, fainting, and, in addition, they gave some evidence of general nervous instability. In the great majority of cases these symptoms antedated enlistment, and often dated back to childhood. Persons presenting these symptoms following some infectious disease were excluded, and in none could a diagnosis of organic cardiac disease be made. In almost all cases, tachycardia and tremor were present at one time or another. The hands were usually cyanosed, cold and clammy. These patients thus seemed to belong to what has been called the constitutional type of irritable heart, or neurocirculatory asthenia. Basal pressure and pulse rate measurements were made on 138 of these patients. In Table 6 the averages, standard deviations and frequency distributions are given.

TABLE 6.—BASAL MEASUREMENTS ON PATIENTS PROVISIONALLY DIAGNOSED AS "IRRITABLE HEART" CASES

Averages

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
105	72	33	65	2145

Standard Deviations

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
±11.8	±10.9	±9.0	±8.9	±706

Coefficients of Variation

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
11%	15%	27%	14%	33%

Frequency Distributions

Systolic		Diastolic		Pulse Pressure		Pulse Rate		P. P. × P. R.	
Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl.Int.	Per Cent.
71- 80	4	31- 40	1	11-20	16	37-44	1	100- 999	2
81- 90	11	41- 50	3	21-30	47	45-52	12	1000-1999	54
91-100	30	51- 60	12	31-40	26	53-60	28	2000-2999	35
101-110	30	61- 70	37	41-50	9	61-68	38	3000-3999	8
111-120	21	71- 80	34	51-60	1	69-76	12	4000-4999	1
121-130	4	81- 90	11	.....		77-84	6		
		91-100	2	.....		85-92	3		
		101-110	1						

The average level of all the measurements on the patients is slightly higher than the basal averages for normals given in Table 1. The greatest increase is in the P. P. × P. R. product. In this case the difference is statistically significant, for when the "probable difference between the averages" is determined the odds are found to be about 64

to 1 against the possibility that the increase from 1,764 for the normals to 2,145 for the patients can have arisen simply as the result of chance. It would appear, then, that some factor not operative in the normal cases had increased the P. P. × P. R. This might have been the inclusion of some cases of hyperthyroidism or the same difference might be due to a greater nervous excitability in the patients. But whatever the cause may have been, it is evidently of relatively slight importance, since all but 1 per cent. of the observations on patients fall within the range of variation of the normal. It seemed to us to be of particular significance that patients whose condition during daytime examinations showed so many points of resemblance to hyperthryroidism should in the early morning, under basal conditions, give evidence of an inactivity and quietude of the circulatory system which seemed inconsistent with the hypothesis of a state of continuing metabolic activity, such as exists in hyperthyroidism. It is true that in individual cases we were sometimes still in doubt, but the important question at the time was one of group diagnosis; and the fact that a normal basal product, as well as a normal basal pulse rate, was found in practically all these patients was of aid, in conjunction with other evidence, in leading us to reject a diagnosis of hyperthyroidism for this group of patients. At a later date Peabody, Wearns and Tompkins [13] showed the correctness of this conclusion by demonstrating that patients of this type, many of whom had been diagnosed as having hyperthyroidism, had an entirely normal rate of basal metabolism.

An increase in the P. P. × P. R. product may be found in patients in whom there is no reason to suspect any increase in the rate of metabolism. This is shown in the daytime measurements given in Table 7.

TABLE 7.—DAYTIME MEASUREMENTS SHOWING INCREASE IN P.P × P.R. PRODUCT

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Normals	127	78	50	80	3980
Patients	190	113	77	79	6083

The patients were nineteen middle aged or old people who had hypertension. They were unselected cases, except that those with cardiac decompensation or advanced renal disease were excluded. There were no indications whatsoever of any increased metabolic activity, rather the reverse. Yet their P. P. × P. R. product is markedly increased, but it is an increase due to a rise in only one factor of the product, the pulse pressure. Furthermore, it has been shown that any decrease in the elasticity of the large vessels between the heart

13. Peabody, Wearn and Tompkins: Med. Clin. N. America **2**:507, 1918.

and the brachial artery will result in an increase in pulse pressure because the pressure will rise higher at each systole, if the vessels are rigid than if they give way to some extent when the blood is forced into them by the heart.[6] Hence, when a product is found to be high only because of an increase in pulse pressure it would be well to suspect the presence of an inelastic aorta, rather than an increased output of the heart.

Daytime measurements were also made on 156 patients who were believed to have an irritable heart. This group includes the 138 persons whose basal pressures and pulse rates were obtained. The averages given in Table 8 are derived from 580 observations.

TABLE 8.—DAYTIME MEASUREMENTS ON PATIENTS PROVISIONALLY DIAGNOSED AS "IRRITABLE HEART" CASES

Averages

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
131	75	55	85	4680

Standard Deviations

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
±18.5	± 11.5	±17.5	±13.4	±1982

Coefficients of Variation

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
14%	15%	32%	16%	43%

Frequency Distributions

Systolic		Diastolic		Pulse Pressure		Pulse Rate		P. P. × P. R.	
Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl.Int.	Per Cent.
71– 80	0.2	31– 40	1	11– 20	1	37– 44	..	0– 999	..
81– 90	0.5	41– 50	2	21– 30	7	45– 52	..	1000– 1999	2
91–100	5	51– 60	10	31– 40	17	53– 60	2	2000– 2999	12
101–110	8	61– 70	26	41– 50	27	61– 68	8	3000– 3999	22
111–120	21	71– 80	35	51– 60	20	69– 76	23	4000– 4999	22
121–130	27	81– 90	21	61– 70	15	77– 84	23	5000– 5999	15
131–140	18	91–100	4	71– 80	6	85– 92	20	6000– 6999	10
141–150	10	101–110	1	81– 90	4	93–100	14	7000– 7999	6
151–160	6	111–120	0.2	91–100	2	101–108	7	8000– 8999	3
161–170	3	.....		101–110	1	109–116	5	9000– 9999	2
171–180	2	.....		111–120	0.2	117–124	1	10000–10999	1
181–190	0.4	.....		121–130	0.2	125–132	1	11000–11999	0.4
191–200	0.5	.....		.....		.....		12000–12999	0.2
								13000–13999	0.2

The averages show a little increase in systolic pressure and pulse rate as compared with the normals—131 as compared with 127. There is also a somewhat greater variability in systolic, diastolic and pulse pressures and P. P. × P. R. in the patients as compared with the controls. But these differences are slight. This is of interest since it will be shown in the next paper that a marked variation from the normal can be demonstrated in this group of patients under conditions which impose a strain on the cardiovascular system.

2. HYPERTENSION IN YOUNG MEN

In eighteen soldiers between 21 and 31 years of age a systolic pressure of more than 150 was found on repeated daytime examinations.

These cases are briefly reviewed here because a comparison of their basal and day measurements brought up a point which may prove to be of some importance. They can be separated into four groups in accordance with the conditions associated with the hypertension.

The first group comprises six cases in which no other evidence of disease than the hypertension was found. The following is a summary of the record of the only case in this group in which cardiac enlargement was found.

CASE 1.—Sa., aged 26; no complaint.

Mother died of heart disease. Measles and diphtheria in childhood. Pneumonia when 8 years old.

Six months ago, while doing heavy work in France, he became breathless on exertion. He reported for examination, and has been kept on light duty since then. Neither before nor since that time has he had any complaint.

The heart appeared to be enlarged and this was confirmed by roentgen-ray examination, which showed an increase in the transverse diameter. There was a systolic murmur best heard over the aortic area and audible in the neck. There was no thrill. The Wassermann was negative.

After restriction of fluids the night urine had a specific gravity of 1.025 on one occasion, and 1.030 on another. No albumin or casts were found. Phenolsulphonephthalein excretion was 80 per cent. in two hours and ten minutes after intramuscular injection.

Ophthalmoscopic examination showed a greater tortuosity than usual in the retinal vessels, but no thickening of the arteries.

TABLE 9.—BASAL AND DAYTIME PRESSURES AND PULSE RATES ON HYPERTENSION CASES NOT ASSOCIATED WITH ANY DISCOVERABLE DISEASE

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Sa.	170	105	65	64	4160	223	115	108	96	10380
Fr.	140	90	50	96	4800	155	80	75	122	9150
W.	133	77	56	80	4480	164	78	86	98	8000
L.	118	73	45	80	3600	164	99	65	91	5910
Sto.	130	80	50	60	3000	156	90	66	91	6006
Stoe.	120	85	35	60	2100	168	95	73	86	6278

The second group includes eight patients who were all typical instances of constitutional neurocirculatory asthemia. The record of the patient Ta is characteristic of this group.

CASE 2.—Ta., aged 28; complains of dyspnea, palpitation, precordial pain, dizziness, frequent fainting and extreme "nervousness." Duration, twelve years or more.

His father is very nervous. His mother is subject to fits. His sister has heart trouble.

The only serious illness he remembers is typhoid fever when he was 16 years old.

He has never been able to do hard work. While he was in Italy he was three times drafted into the army, but each time he was discharged on account of disability.

The heart showed no evidence of enlargement. There was a faint systolic murmur at the apex. The pulse rate was always regular, but usually rapid. The hands were often blue and cold and there was a marked tremor. There was no enlargement of the thyroid or protrusion of the eyes. The urine contained no albumin or casts.

TABLE 10.—Basal and Daytime Pressures and Pulse Rates on Hypertension Cases Associated with Neurocirculatory Asthenia (Irritable Heart)

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Ta.	125	70	55	80	4400	160	91	69	91	6490
R.	135	98	42	72	3024	158	106	52	96	4980
Sch.	130	110	20	84	1680	175	106	69	124	8550
O.	120	70	50	60	3000	154	72	82	90	7380
Fri.	120	90	30	72	2160	157	88	69	88	5720
Greenw.	113	80	33	72	2380	177	97	80	90	7200
Greenb.	110	80	30	72	2160	162	97	65	97	6305

The third group contains two cases associated with active pyogenic infection.

Case 3.—Ri. had experienced some shortness of breath and palpitation on exertion two years before, but these symptoms had been greatly aggravated following a mastoid and frontal sinus infection from which he was still suffering.

Case 4.—Ch. also complained of most of the symptoms experienced by the irritable heart group, but he had a pronounced infection of the urinary tract associated with evidences of renal decompensation. His urine contained much pus and was always of low specific gravity even after restriction of fluids. His phenolsulphonephthalein excretion was 15 per cent., two hours and ten minutes after intramuscular injection. After intravenous injection, 8 per cent. was excreted in sixteen minutes from the left kidney and none from the right. Pus was seen coming from both ureters. No tubercle bacilli were found.

TABLE 11.—Basal and Daytime Pressures and Pulse Rates on Hypertension Cases Associated with Pyogenic Infections

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Ri.	135	90	45	68	3060	172	108	64	84	5380
Chi.	132	75	67	68	4556	160	72	88	80	7040

In the last group there are two cases with advanced Bright's disease.

Case 5.—R. was 21 years old. He complained of occasional headaches.

He had scarlet fever when a child. Two years ago his ankles were swollen and painful for some weeks, and a year ago there was a recurrence of this condition.

There was a diffuse retinitis in both eyes. The urine contained a moderate amount of albumin. The specific gravity never rose above 1.016 in spite of fluid restriction. The sediment showed coarsely granular and highly refractile casts, many of them three to four times broader than the usual cast. Only a trace of phenolsulphonephthalein was excreted. The blood urea concentration was 171 mg. per hundred c.c.

CASE 6.—C. also complained of occasional headaches. His urine contained a moderate amount of albumin, and the sediment showed a fair number of blood casts. The phenolsulphonephthalein excretion was 25 per cent. in two hours and ten minutes.

TABLE 12.—BASAL AND DAYTIME PRESSURES AND PULSE RATES ON HYPERTENSION CASES ASSOCIATED WITH ADVANCED BRIGHT'S DISEASE

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
R.	169	118	51	60	3060	173	123	50	69	3450
C.	148	120	28	59	1652	167	107	60	66	3960

Only a few of the basal measurements on these patients would have been regarded as unusual if the low average pressure and narrow range of variation of normal individuals had not been known. But taking all these figures together, the average systolic pressure in the early morning is 32 mm. above the normal basal average as compared with a daytime systolic pressure 40 mm. in excess of the normal daytime average. As a whole, then, these hypertension cases, selected because of their high daytime systolic pressures, still showed hypertension in the early morning when the pressor stimuli of the day were no longer in action. The point, however, which seems to me to be of special clinical significance is the wide variation in the degree of reduction of pressure during the night shown by the different individuals of this series. The first case in Group I and the two nephritic cases are distinguished from the others by the relatively slight decrease of pressure in the early morning and especially by the maintenance of high diastolic pressures. In a large series of cases it might be possible to distinguish two types of hypertension, one in which there is a pronounced fall in pressure under basal conditions and another in which the decrease is only slight. It is true that such a distinction would be one of degree only and would not necessarily depend on any difference in etiology. But from the point of view of prognosis it is surely of importance. In the patient Greenw., for instance, the average daytime pressure of 177 systolic and 97 diastolic will be more easily borne than the systolic of 167 and the diastolic of 107 in the patient C. with Bright's disease, because in the first case the cardiovascular system is rested each night by the fall to the basal levels of 113 and 80, whereas in the renal case there is no remission, and the heart has continually to work against a high diastolic pressure.

SUMMARY

1. The blood pressure and pulse rate of normal persons were measured under what are called basal conditions, i. e., in the early morning before the subjects had risen from bed or taken food. These results

are contrasted with similar measurements on normal persons under what are called daytime conditions, i. e., at any time during the day after the subjects had risen from bed and had had food, but in all cases in the recumbent position and with the exclusion of those who had recently undergone any muscular exertion, such as stair climbing or drilling. The averages obtained are shown in Table 13.

TABLE 13.—AVERAGES OF PULSE PRESSURE AND PULSE RATE

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	99	71	28	63	1764
Day time	127	78	50	80	3980

2. The variability of normal basal and daytime pressures and pulse rates is defined by statistical methods and probability tables for use in clinical work are given.

3. The significance of the difference between basal and daytime pressures and pulse rates is discussed, and data on the influence of exercise and of psychic disturbance on pressure and pulse rate levels are given.

4. Measurements of basal and daytime levels were made on patients, and the deductions which may be drawn from comparison with the normal data are discussed.

BOOK REVIEWS

DIAGNOSTISCHE WINKE FUR DIE TAGLICHE PRAXIS. Dr. E. Graetzer. Verlag von S. Karger, Berlin, 1920.

Books of this type are intended for the medical student and the general practitioner. They have a certain value and are a type of reference a busy and perplexed practitioner will most readily consult. This text will appeal because it deals largely with the atypical forms and symptoms of various diseases. These are given in considerable detail. A brief résumé of the normal train of symptoms of a given disease precedes the description of the atypical forms. This should prove a valuable feature of the book. Differential diagnoses are generally only mentioned. It is obviously difficult and probably hardly intended that a text of this kind should cover any subject in detail. Its function is limited and chiefly lies in the fact that it serves as a quick reference and that it emphasizes the unusual features of a given disease. The frequent allusions throughout the book to other sources of reference should prove very helpful.

THE EVOLUTION OF DISEASE. By Prof. J. Danysz. Translated by Francis M. Rackemann, M.D. Philadelphia: Lea & Febiger, 1921.

The subtitle of Professor Danysz' book, which is "A Discussion of the Immune Reactions Occurring in Infectious and Noninfectious Disease. A Theory of Immunity, of Anaphylaxis and of Antianaphylaxis," indicates, in a general way, the scope of the subject matter. In effect, it is an argument for the selective rather than the specific action in the process of immunity and anaphylaxis. Throughout most of the book the reviewer follows the argument with considerable interest. As long as the discussion is largely theoretical, in spite of the fact that it is an illustration of special pleading, and that it is somewhat involved with specialized terms, the argument is somewhat convincing. The effect of the illustrative cases reported by Professor Danysz, many of which are tactfully omitted by the translator, is, however, to shake the confidence in the earlier theoretic discussion. The results from the administration of a bacterial vaccine derived from certain bacteria of the intestinal flora in a wide variety of conditions, including neurasthenia, psoriasis, and asthma, are too strikingly successful. It should be stated, however, that Danysz particularly emphasizes the fact that the successful issue in these cases is not dependent on the theoretical assumption of any specific therapy, but depends rather on the theoretic assumption of a selective action of these bacterial antigens. Furthermore, Danysz does not believe that these conditions are due to any of the components of the bacterial antigens. The book represents an interesting speculation on the nature of the obscure processes of immunity and anaphylaxis, rather than the record of scientific achievement, or of sound application of the theory.